The Use of Steric Auxiliaries in Nitrile Oxide Cycloadditions

by

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of

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Declaration

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.....S J Barrow.....

Stuart J. Barrow

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Finally, I'd like to thank my wife, Jenny. It's no exaggeration to say that without her, I wouldn't have made it. Love you.

Stuart Barrow, Feb 1999.

Publications

Some of the work described in this thesis has been reported in the following publications.

1. Exploiting the 1,3-Dithiane of 2-Oxopropanenitrile Oxide in 1,3-Dipolar Cycloaddition Reactions.

   Barrow, S.J., Easton, C.J.; Savage, G.P.; Simpson, G.W.; *Tetrahedron Letters*, **1997**, *38*, 2175-2168

2. Mechanistic Studies of Nitrile Oxide Dimerisation.

   Barrow, S.J; Easton, C.J.; Savage, G.P.; Simpson, G.W.; Presented at: 15th National Organic Conference, RACI, Division of Organic Chemistry, Yeppoon, June-July 1996.

3. The Use of Steric Auxiliaries in Nitrile Oxide Cycloadditions.

   Simpson, G.W.; Savage, G.P.; Easton, C.J.; Barrow, S.J.; Presented at: Southern Highlands Conference on Heterocyclic Chemistry, Bowral, NSW, September 1997.

4. Steric Auxiliaries in Nitrile Oxide Cycloaddition Reactions.

   Barrow, S.J; Easton, C.J.; Savage, G.P.; Simpson, G.W.; Presented at: 16th National Organic Conference, RACI, Division of Organic Chemistry, Leura, July 1998.

Abstract

The 1,3-dipolar cycloaddition of nitrile oxides is a reaction of some synthetic utility. The dimerisation of nitrile oxides to form 3,4-disubstituted furoxans is a competing reaction to this cycloaddition. The aim of this work was to investigate methods of circumventing this dimerisation.

The cycloreversion of 3,4-disubstituted furoxans to 2 equivalents of nitrile oxide was investigated. This reaction was shown to require high temperatures to proceed, and resulted in large proportions of decomposition products.

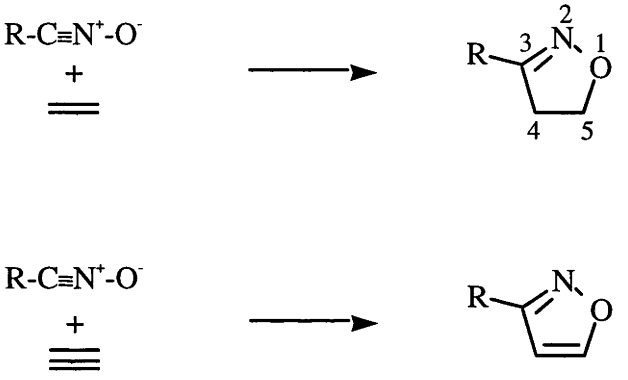
A model system for the tethering of nitrile oxides to a solid support using solid-phase peptide synthetic techniques was also investigated. Nitro-substituted carboxylic acids were found to be unreactive under the conditions used for the generation of nitrile oxides from primary nitroalkanes.

The synthesis and stability of a number of alkylnitrile oxides were examined. Increasing the steric bulk of a nitrile oxide was found to prolong the lifetime of the nitrile oxide by preventing dimerisation. However, propanenitrile *N*-oxide was found to be more stable than is implied in the literature. Conversely, 2-oxopropanenitrile *N*-oxide was found to be considerably less stable than expected. The increased stability of sterically hindered nitrile oxides was exploited by the synthesis of nitrile oxides containing a removable 1,3-dithiane moiety, which led to an increase in stability over acyl- and primary alkyl-nitrile oxides. This synthesis was general and allows for the synthesis of a range of 2-substituted-1,3-dithiane-2-carbonitrile *N*-oxides.

The utility of the 1,3-dithiane as a steric auxiliary was investigated. The increased stability of the 1,3-dithianenitrile oxides allowed a greater extent of cycloaddition than 2-oxopropanenitrile *N*-oxide. The removal of this moiety was effected by reductive and hydrolytic methods. The hydrolysis of cycloadducts of 1,3-dithiane nitrile oxides led to 3-acyl isoxazolines that are unavailable *via* the cycloaddition of acyl nitrile oxides.

Chapter 1: Introduction

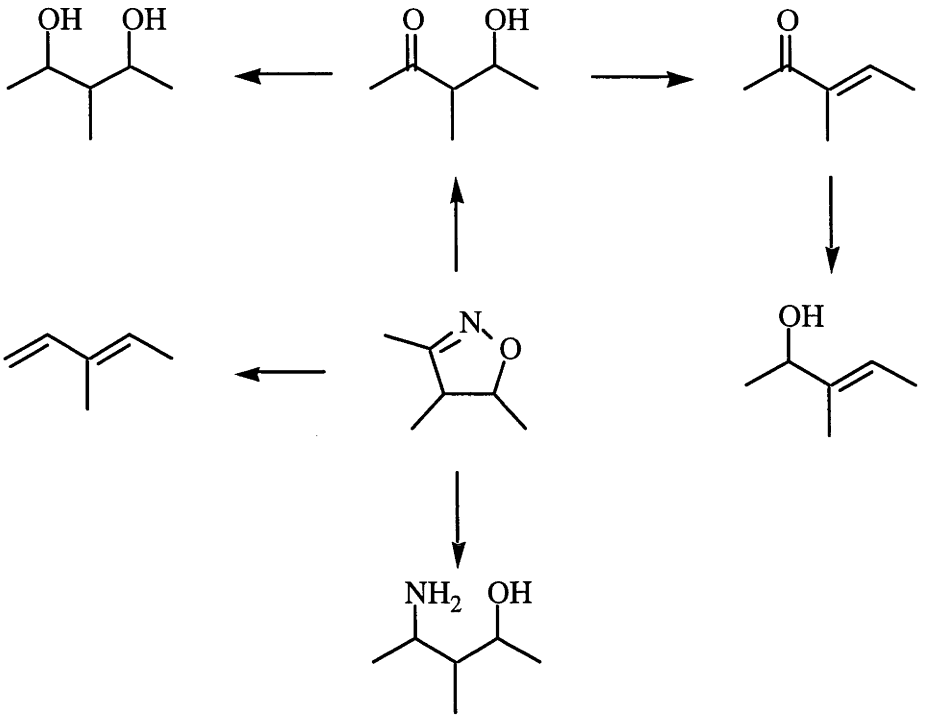
The reaction of nitrile oxides with unsaturated centres (Scheme 1) has become a popular method of synthesising Δ^2-isoxazolines (hereafter referred to as isoxazolines) and isoxazoles. The reaction was first reported in 1950 by Quilico and coworkers.[1, 2]



Scheme 1

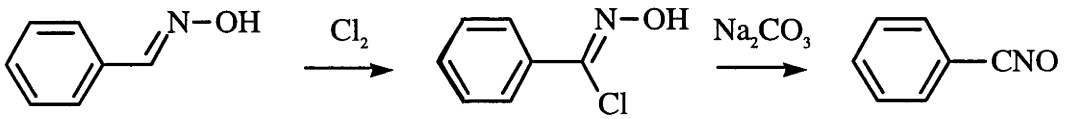
Isoxazolines and isoxazoles are of considerable interest to synthetic chemists as intermediates in the synthesis of a wide range of polyfunctional molecules.[3-9] An indication of the more general procedures is shown in Scheme 2. Molecules available from isoxazolines include γ-amino alcohols,[10, 11] β-hydroxy ketones,[12, 13] α,β-unsaturated ketones and β,γ-unsaturated alcohols.[3, 6, 14]

This reaction of nitrile oxides with unsaturated centres is a 1,3-dipolar cycloaddition reaction, belonging to the broad class of [3+2] cycloaddition reactions as categorised by Huisgen.[15-17] The cycloaddition proceeds with retention of stereochemistry about a double bond and a moderate to high degree of regioselectivity.



Scheme 2

1.1 Nitrile Oxide Generation



(1) **(2)** **(3)**

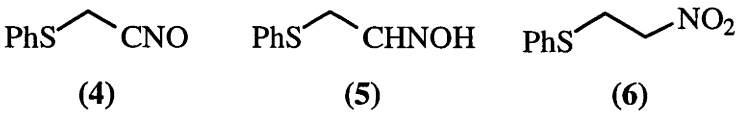
Scheme 3

Benzonitrile oxide (**3**) was synthesised in 1894 by Werner and Buss[18] from benzaldoxime (**1**) by chlorination to give the hydroximinoyl chloride (**2**), followed by dehydrohalogenation with sodium carbonate (Scheme 3). This method still forms the basis of one of the most common nitrile oxide syntheses. Chlorination has been effected using a number of different reagents, including hypochlorites,[19, 20] chloramine-T,[21] and *N*-chlorosuccinimide.[22, 23] As a variation of this method of synthesis, nitrile oxides can also be generated from hydroximinoyl bromides, which have been prepared from oximes using reagents such as hypobromite,[24] sodium bromite with a tributyltin chloride catalyst,[25] and

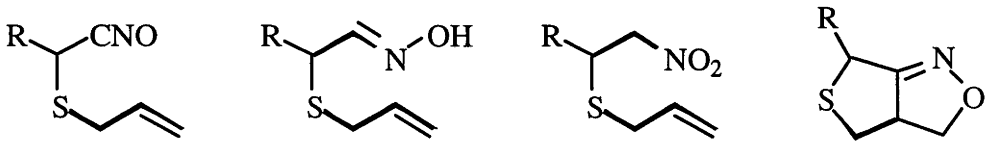
N-bromosuccinimide.[26] Elimination of hydroximinoyl halides has been effected using a variety of bases, particularly tertiary amines,[27] but including aluminium oxide,[28] molecular sieves,[29] hexabutylditin[30] and alkali metal fluorides.[31] The nitrile oxide can also be formed by direct oxidation of an oxime using reagents such as dimethyldioxirane[32] and lead tetraacetate.[33, 34]

Scheme 4

Another common method of nitrile oxide generation involves the dehydration of primary nitroalkanes using phenyl isocyanate in the presence of a catalytic amount of triethylamine (Scheme 4).[35] This procedure is often referred to as the Mukaiyama reaction. Other dehydrating agents have been used, such as phosphorus oxychloride,[36] chloroformate esters,[37] aryl-[37,38] and alkyl-sulfonyl chlorides,[39] acetic acid and acetic anhydride.[39] The



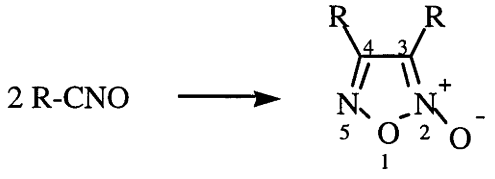
(4) **(5)** **(6)**



(7) **(8)** **(9)** **(10)**

dehydration method has been used to generate nitrile oxides containing moieties which are susceptible to oxidation, such as the sulfide-containing nitrile oxides (**4**) and (**7**).[19, 40] Treatment of the oxime (**5**) with sodium hypochlorite and triethylamine resulted in a considerably less efficient generation of the nitrile oxide (**4**) than did the dehydration of the primary nitroalkane (**6**) with phenyl isocyanate. This was demonstrated using trapping experiments with a range of dipolarophiles, including styrene, 1-heptene and

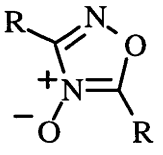
3-chloropropyne.[19] Similarly, the oximes (**8**) (R = alkyl, aryl) were found to be sensitive to sodium hypochlorite and chloramine-T, while the nitrile oxides (**7**) could be generated from the primary nitroalkanes (**9**). The nitrile oxides (**7**) then undergo intramolecular cycloadditions to give the bicyclic compounds (**10**).[40]



(11)

Scheme 5

The synthetic utility of nitrile oxides is somewhat limited by their tendency to dimerise to give 3,4-disubstituted furazan *N*-oxides, known as furoxans (**11**), as depicted in Scheme 5. The alternative regioisomers, the 3,5-disubstituted-1,2,4-oxadiazoles (**12**) and the 3,6-disubstituted-1,4,2,5-dioxadiazines (**13**), have not been observed in the direct dimerisation of nitrile oxides. Both of the alternative isomers (**12**) and (**13**) are accessible



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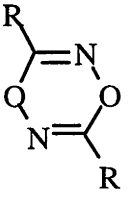
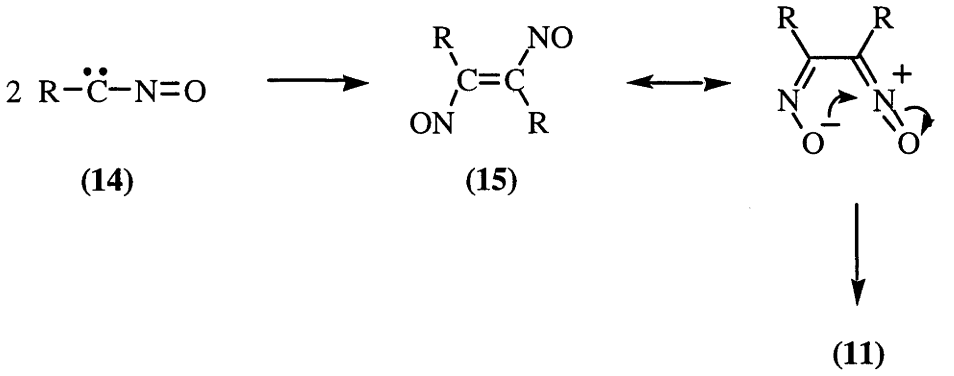


(13)

via acid-catalysed dimerisation of nitrile oxides,[41] and the isomers (**13**) are available by based-catalysed dimerisation.[42] While it is tempting to regard the nitrile oxide dimerisation shown in Scheme 5 as a 1,3-dipolar cycloaddition, it shows a number of differences to the standard reactions of this type. The orientation of the dimerisation is counter to that expected from other nitrile oxide cycloadditions. The cycloaddition of nitrile oxides with unsaturated centres containing heteroatoms generally proceeds in accordance with the principle of maximum gain in σ-bond energy, as stated by Huisgen,[17] such that the heteroatom is in the 4- rather than the 2-position of the resultant heterocycle. If

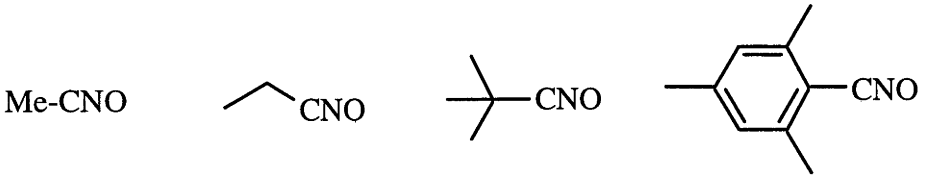
dimerisation proceeded *via* a 1,3-dipolar cycloaddition, this principle would suggest a preference for the 1,2,4-oxadiazoles (**12**) over the furoxans (**11**). Steric considerations also suggest a preference for the 1,2,4-oxadiazoles (**12**). Clearly, the steric interactions between the substituents R are much greater in the furoxan (**11**) than in the 1,2,4-oxadiazoles (**12**).



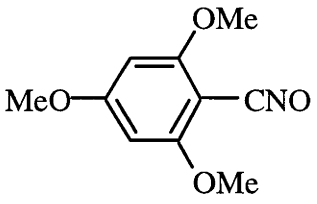
(14) **(15)** **(11)**

Scheme 6

An alternative mechanism for nitrile oxide dimerisation has been proposed to account for these observations (Scheme 6).[17, 43] According to this mechanism, dimerisation proceeds *via* the dinitrosoethylene (**15**). This is presumed to occur with the nitrile oxide reacting as a carbene, as represented by the resonance form (**14**). The intermediate (**15**) cyclises to form the furoxan (**11**). This mechanism has been supported by a semiempirical MNDO calculation by Kurdyukov and coworkers,[44] in which the dinitrosoethylene (**15**) (R = CH_3) was shown to be the likely intermediate in the dimerisation of ethanenitrile oxide (**16**).



(16) **(17)** **(18)** **(19)**



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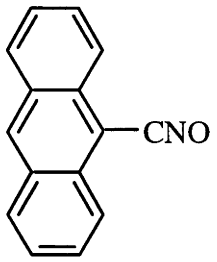

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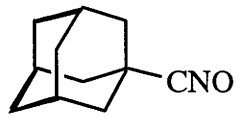
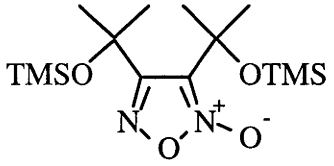


(22)

A large steric bulk has been shown to lead to a slower rate of dimerisation. Nitrile oxides possessing little steric bulk such as ethanenitrile *N*-oxide (**16**) and propanenitrile *N*-oxide (**17**) have been detected and isolated at low temperature, but are generally reported to dimerise immediately at room temperature.[45-47] Nitrile oxides such as 2,2-dimethylpropanenitrile *N*-oxide (**18**) and benzonitrile oxide (**3**) have observable lifetimes. 2,2-Dimethylpropanenitrile *N*-oxide (**18**) dimerises over the course of 2-3 days in the solid state at 18°C,[46, 48] and has a half-life of dimerisation of about 9 days at a concentration of 0.2 M in d_6-benzene at room temperature.[12] Benzonitrile oxide (**3**) dimerises in 30-60 minutes in the solid state at 18°C,[48] and over several days in a carbon tetrachloride solution of approximately 0.1 M at 40°C.[49] Electron withdrawing substituents on the aromatic ring in either the *meta*- or *para*-position result in an increase in the rate of dimerisation, while electron donating substituents in these positions decrease the rate of dimerisation.[49] Usually, however, only arylnitrile oxides substituted with groups of large steric bulk in the 2- and 6-positions are sufficiently stable to allow isolation at room temperature. For example, mesitylnitrile *N*-oxide (**19**), 2,4,6-trimethoxybenzenecarbonitrile *N*-oxide (**20**) and anthracene-9-carbonitrile *N*-oxide (**21**) do not dimerise at room temperature.[24] Adamantanecarbonitrile *N*-oxide (**22**) is reported as one of the few stable alkylnitrile oxides known, and does not dimerise at room temperature.[50] Despite their inactivity towards dimerisation, these nitrile oxides retain cycloaddition activity.[24, 43, 50]

Apart from through the use of sterically hindered nitrile oxides, dimerisation can also be reduced by keeping a low concentration of nitrile oxide in order to facilitate

competing cycloaddition to an alkene. This is usually done by generating the nitrile oxide *in situ*, in the presence of excess alkene.[16] The extent of competing dimerisation can be further reduced by using low reaction temperatures or by the slow addition of reagents.[16, 45]



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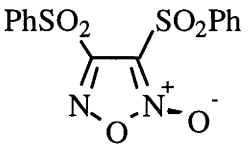

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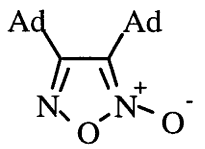

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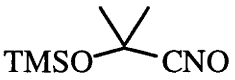

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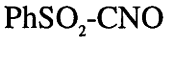

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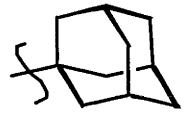
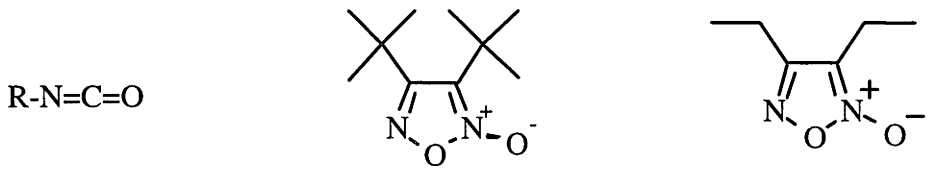


Nitrile oxides have also been generated by thermal decomposition of furoxans.[51-57] Obviously, dimerisation ceases to be a problem under these conditions. Both benzonitrile *N*-oxide (**3**) and ethanenitrile *N*-oxide (**16**) have been synthesised from the corresponding furoxans using flash vacuum pyrolysis.[51] However, at high temperatures, which are generally required for cycloreversion of furoxans, nitrile oxides are known to undergo intramolecular rearrangement to form isocyanates (**28**),[45, 58-60] limiting the effectiveness of this procedure. The cycloreversions of some furoxans have been observed under relatively mild conditions, notably 3,4-bis[2-[(trimethylsilyl)oxy]prop-2-yl]furoxan (TOP-furoxan) (**23**),[61] 3,4-bis(benzenesulfonyl)furoxan (**24**) [56] and 3,4-diadamantanylfuroxan (**25**).[50] Cycloreversion of TOP-furoxan (**23**) occurs at 165°C (benzene, sealed tube). The resultant nitrile oxide (**26**) can be trapped in good yield using a range of dipolarophiles. The presence of the isocyanate derivative is not observed. Cycloreversion of bisbenzenesulfonylfuroxan (**24**) occurs at 140°C (xylene, reflux). The resultant nitrile oxide (**27**) can similarly be trapped using a range of dipolarophiles, albeit in more moderate yields. 3,4-Diadamantanylfuroxan (**25**) undergoes cycloreversion to adamantanecarbonitrile *N*-oxide (**22**) under very mild conditions; the nitrile oxide (**22**) is formed at 76°C (carbon tetrachloride, reflux). However, under these conditions,

adamantanecarbonitrile *N*-oxide (**22**) still readily isomerises to the isocyanate, such that a large excess of dipolarophile is required to ensure a good yield of cycloaddition. The cycloreversion is favoured by relief of steric strain; Curran and co-workers[61] found that 3,4-diethylfuroxan (**30**) did not undergo cycloreversion at 200°C, while 3,4-di-*tert*-butylfuroxan (**29**) showed similar cycloreversion properties to TOP-furoxan (**23**), undergoing cycloreversion at 135°C (benzene, sealed tube).



(28) **(29)** **(30)**

1.2 Cycloadditions of Nitrile Oxides

The mechanism of the nitrile oxide cycloaddition reaction has been the subject of some scrutiny. The generally accepted mechanism is a one-step, concerted reaction (illustrated in Figure 1),[62, 63] as described by the Sustmann frontier molecular orbital (FMO) theory.[64] According to the Sustmann model, the reactivity of a dipole with a dipolarophile can be rationalised by analysis of the energy separations between the highest occupied and lowest unoccupied molecular orbitals.

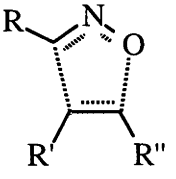


Figure 1: Illustration of the concerted nature of the 1,3-dipolar cycloaddition of nitrile oxides with dipolarophiles.

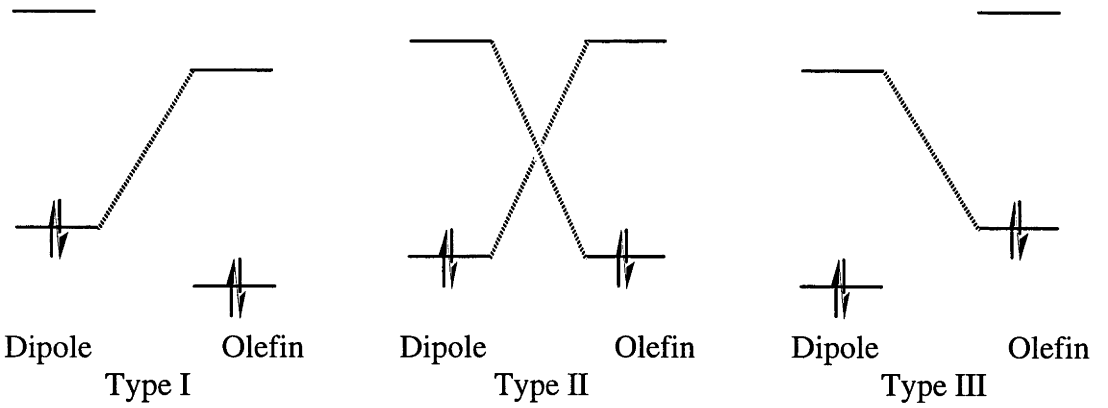


Figure 2: Sustmann classification of the FMOs for the interaction of nitrile oxides with olefins.[64]

Cycloadditions are divided into three categories, as represented in Figure 2:

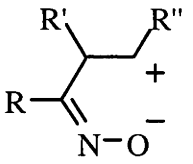
Type I: The cycloaddition involves the interaction of the highest occupied molecular orbital (HOMO) of the nitrile oxide with the lowest unoccupied molecular orbital (LUMO) of the olefin.

Type II: The cycloaddition involves both the interaction of the HOMO of the nitrile oxide with the LUMO of the olefin, and the LUMO of the nitrile oxide with the HOMO of the olefin.

Type III: The cycloaddition involves the interaction of the LUMO of the nitrile oxide with the HOMO of the olefin.

In each category, the reactivity is inversely proportional to the difference in energy between the interacting orbitals. Electron donating substituents on the dipolarophile raise the frontier orbital energies, decreasing the reactivity in Type I systems while increasing the reactivity in Type III systems. Electron withdrawing substituents have the opposite effect, lowering the frontier orbital energies and hence increasing reactivity in Type I systems and decreasing reactivity in Type III systems. The effect of olefin substitution on Type II systems depends on which interaction becomes dominant. Conjugation of the dipolarophile results in an increase in the HOMO energy and a decrease in the LUMO energy, increasing the reactivity of Type I, II and III systems. The effect of substituents on

the nitrile oxide can be rationalised in a similar manner. Electron donating substituents favour Type I systems, while electron withdrawing substituents favour Type III systems.



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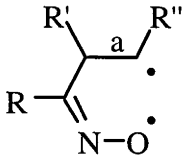


(32)

Mechanisms for the cycloaddition involving a stepwise reaction *via* zwitterion **(31)**[45] and diradical **(32)**[65] intermediates have been proposed. While there is no direct evidence for any of these mechanisms, the fact that the cycloaddition proceeds with retention of the stereochemistry of the dipolarophile is considered compelling evidence for the one-step, concerted mechanism. If a diradical intermediate of the type **(32)** was involved, the reaction would proceed with retention of stereochemistry only if the energy barrier towards cyclisation was significantly (at least 2.3 kcal/mol) lower than that towards the rotation of the bond marked 'a'. A product study by Houk and Firestone[66] in which the reaction of *p*-nitrobenzonitrile *N*-oxide with *cis*- and *trans*-1,2-dideuterioethylene was examined showed that the reaction proceeds with complete retention of stereochemistry about the alkene. In the case of 1,2-dideuterioethylene, the energy barrier towards rotation of the bond marked 'a' is so small (0.1-0.4 kcal/mol) that the energy barrier towards cyclisation would have to be non-existent (or negative!) in order to explain the observed results. Therefore, the authors of this study conclude that a one-step, concerted mechanism is the most likely. Calculations supporting this mechanism[67-69] suggest an asynchronous transition state, in which there is somewhat more C-C than C-O bonding.

The regioselectivity of the cycloaddition of nitrile oxides to alkenes has been rationalised using perturbation theory.[70, 71] The transition state of the cycloaddition is stabilised by the interactions of the orbitals of the dipole and the dipolarophile. The greatest stabilisation is brought about by the interaction of the orbitals with the largest molecular orbital coefficients. For a nitrile oxide, the larger molecular orbital coefficient

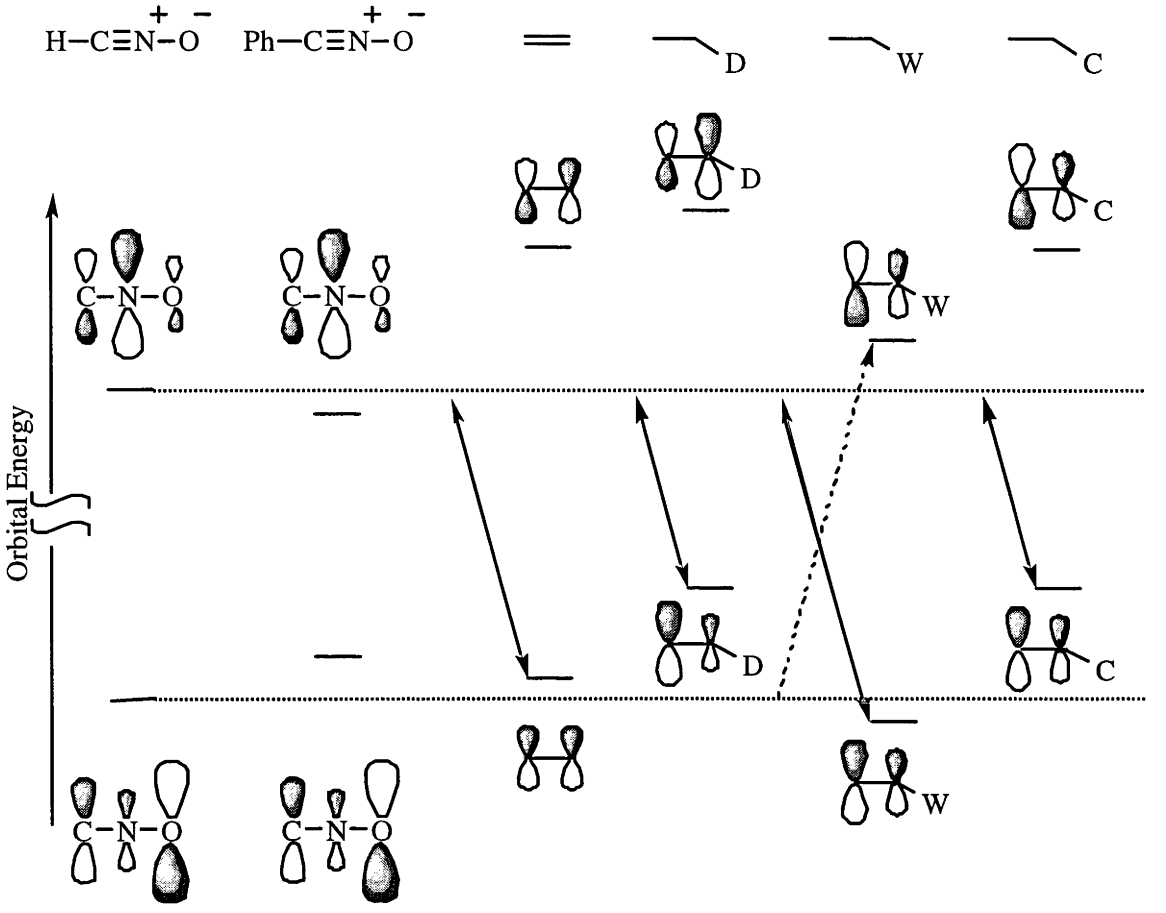
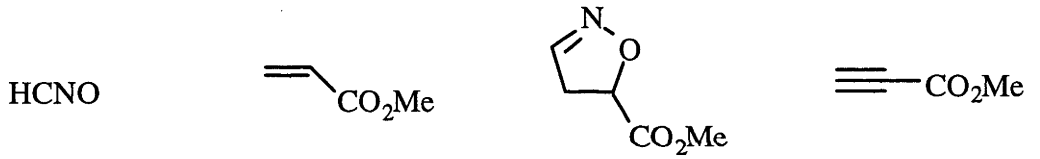


Figure 3: Schematic representation of the frontier molecular orbitals of formonitrile *N*-oxide (33), benzonitrile *N*-oxide (3), ethylene and monosubstituted alkenes.[70, 71]

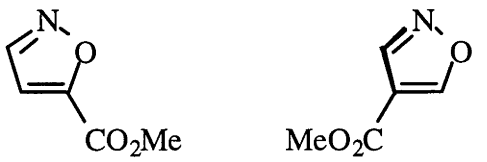
involved in the cycloaddition is on the terminal oxygen in the HOMO and the carbon in the LUMO.[72] For monosubstituted alkenes, the largest coefficient in the HOMO has been identified as being on the terminal carbon for most cases. For monosubstituted alkenes with electron withdrawing substituents W or conjugating substituents C (eg. CO_2R or Ph), the largest coefficient in the LUMO is on the terminal carbon, while for alkenes with electron donating substituents D (eg. NR_2, OR), the largest coefficient in the LUMO is on the substituted carbon.[72]

Using formonitrile *N*-oxide **(33)** and benzonitrile *N*-oxide **(3)** as model compounds, the frontier orbital energies governing these cycloadditions were calculated. These values are represented schematically in Figure 3. Using these values, the cycloadditions of these nitrile oxides were classified as dipole LUMO-controlled (Type III) cycloadditions.

Consequently, cycloadditions to monosubstituted alkenes with electron donating or conjugating substituents are always directed in favour of 5-substituted isoxazolines. Cycloadditions of nitrile oxides to alkenes with electron withdrawing substituents are also directed in favour of 5-substituted isoxazolines. However, due to the lower energy level of the molecular orbitals in alkenes with electron withdrawing substituents, a certain amount of dipole HOMO-control is sometimes observed, resulting in the appearance of small amounts of 4-substituted isoxazolines.[70, 73] The lower frontier orbital energies of alkynes allow an increase in dipole HOMO-control. The cycloaddition of formonitrile *N*-oxide (**33**) to methyl acrylate (**34**) gives methyl isoxazoline-5-carboxylate (**35**) exclusively. The cycloaddition of the same nitrile oxide (**33**) to methyl propiolate (**36**) results in an 84:16 mixture of the 5- and 4-methoxycarbonylisoxazoles (**37**) and (**38**), as a result of the increased amount of dipole HOMO-control.[74]



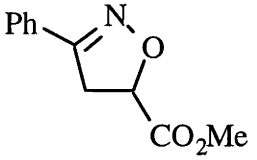
(**33**) (**34**) (**35**) (**36**)



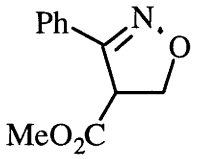
(**37**) (**38**)

This molecular orbital model does not take into account steric considerations. In practice, the majority of 1,3-dipolar cycloadditions to monosubstituted and 1,1-disubstituted alkenes proceed in favour of the 5-position of the isoxazoline becoming the more substituted site regardless of electronic considerations.[75, 76] The cycloaddition of benzonitrile *N*-oxide (**3**) to methyl acrylate (**34**) results in a 96:4 ratio of the 5- and 4-substituted isoxazolines (**39**) and (**40**). Cycloadditions of benzonitrile *N*-oxide (**3**) to

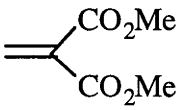
dimethyl methylenemalonate (**41**) and methyl methacrylate (**42**) result in only the 5-substituted isoxazolines (**43**) and (**44**) respectively.[74, 73]



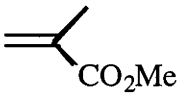
(**39**)



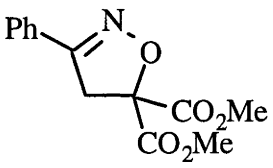
(**40**)



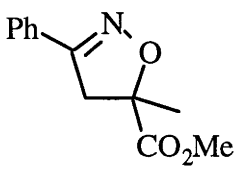
(**41**)



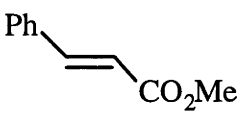
(**42**)



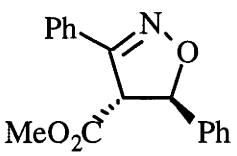
(**43**)



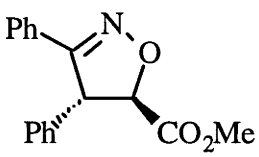
(**44**)



(**45**)



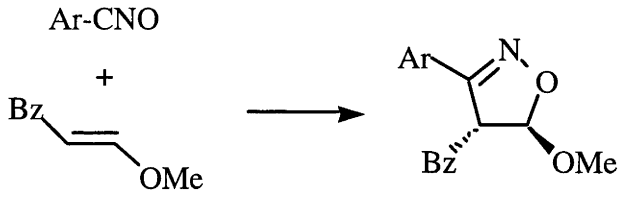
(**46**)



(**47**)

Cycloadditions of nitrile oxides to 1,2-disubstituted alkenes are governed by a combination of steric and electronic factors. Cycloadditions of this type usually result in a mixture of regioisomers, with preference for one isomer determined by the steric and electronic nature of the dipolarophile. As an example, cycloaddition of benzonitrile *N*-oxide (**3**) to methyl cinnamate (**45**) results in a mixture of the 4- and 5-methoxycarbonylisoxazolines (**46**) and (**47**) in the ratio 70:30.[74] As described above, the ratio for the cycloadducts of benzonitrile *N*-oxide (**3**) with methyl acrylate (**34**) is 96:4 in favour of the 5-methoxycarbonylisoxazoline (**39**). On the other hand, the cycloaddition of a series of arylnitrile oxides to the enol-ether (**48**) is regioselective, as a result of the combined electron-donating and electron-withdrawing effects of the substituents (Scheme 7).[77] The electronic effects of substituents on cycloadditions are generally consistent with Houk's frontier orbital model as described above, except where large steric effects are involved. The effects of substituents on the HOMO of an alkene can be described

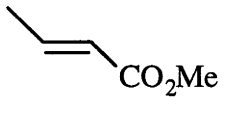
qualitatively as follows: electron-withdrawing substituents exhibit a preference for being in the 4-position of the resultant isoxazoline, while electron-donating substituents prefer orientation to the 5-position of the isoxazoline.



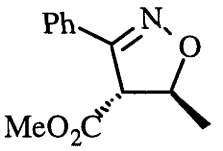
(48)

Scheme 7

The steric effects of the 1,3-dipolar cycloaddition to 1,2-disubstituted alkenes are such that the substituent on the nitrile oxide will interact unfavourably with the substituents of the alkene. Therefore, the smaller, unsubstituted oxygen will become aligned with the most hindered centre of the dipolarophile preferentially, such that the most sterically demanding group substituted to the alkene is in the 5-position of the formed isoxazoline.



(49)



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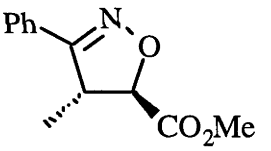
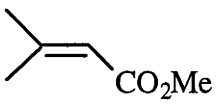
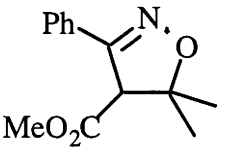


(51)

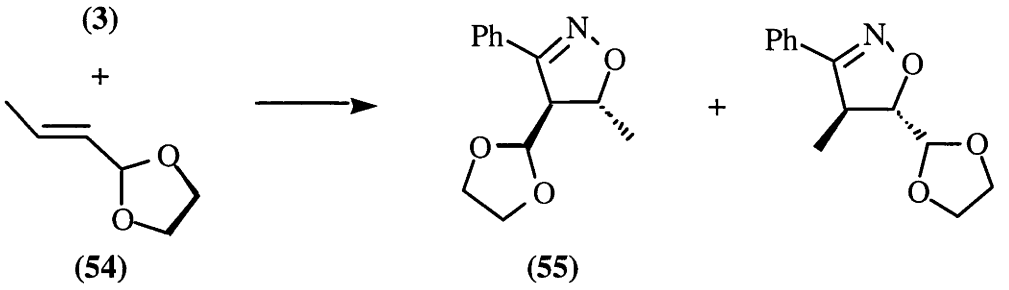


(52)



(53)

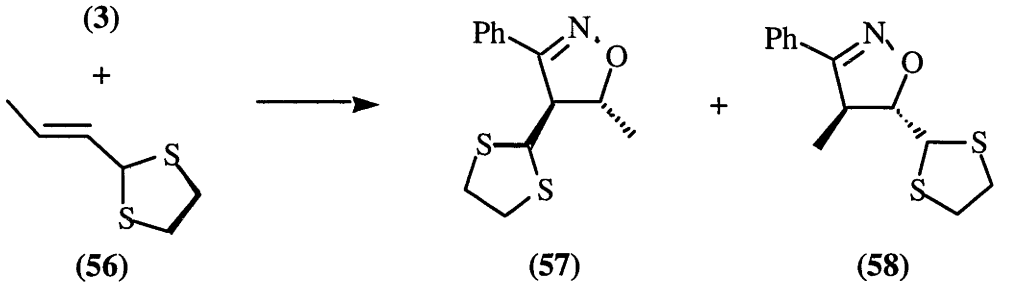
The regiochemistry of cycloadditions to trisubstituted alkenes is almost completely sterically controlled. For example, whereas the cycloaddition of benzonitrile *N*-oxide (**3**) to methyl crotonate (**49**) gives a ratio of the 4- and 5-methoxycarbonylisoxazolines (**50**) and (**51**) of 66:34,[76, 78] the cycloaddition of benzonitrile *N*-oxide (**3**) to methyl 3,3-dimethylacrylate (**52**) gives exclusively the 4-methoxycarbonylisoxazoline (**53**).[4, 79]



(55)

2 : 1

Scheme 8



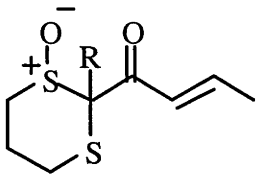
(57) (58)

1 : 3

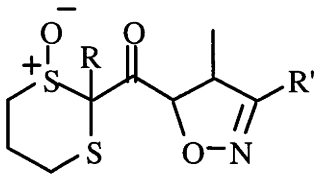
Scheme 9

An interesting case in which the regioselectivity is extremely sensitive to steric effects was presented by Kamimura and Hori.[80] In this case, cycloadditions of nitrile oxides to α,β-unsaturated acetals, such as the crotonaldehyde derivative (**54**), show a preference for the 4-acetal-substituted isoxazolines such as (**55**) (Scheme 8). This observation is consistent with the calculated frontier molecular orbital predictions. However, despite the similarities in electronic nature, cycloadditions to α,β-unsaturated-thioacetals such as the compound (**56**) show the opposite regioselectivity, counter to the frontier molecular orbital predictions (Scheme 9). The steric strain was calculated to be lower in the 5-thioacetal-substituted isoxazoline (**58**) than in the 4-thioacetal-substituted isoxazoline (**57**) by 4.2 kcal/mol. This led the authors to the conclusion that while FMO interactions control the regioselectivity of cycloadditions of nitrile oxides to α,β-unsaturated acetals, steric interactions control the regioselectivity of nitrile oxide cycloadditions to α,β-unsaturated thioacetals.

Unusually, complete regiocontrol is also observed in the cycloadditions of a range of aryl- and alkyl-nitrile oxides to a series of 2-crotyl-1,3-dithiane-1-oxides (**59**).[81] Only the 5-acyl isomers (**60**) are observed, despite the preference of cycloadditions of similar nitrile oxides to methyl crotonate for the 4-methoxycarbonyl isomer.[76, 78]



(**59**)

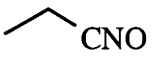


(**60**)

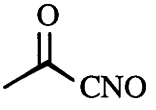
1.3 Aim

1.3.1 General

This project was carried out in order to investigate methods of alleviating dimerisation as a competing reaction in the cycloaddition of alkylnitrile *N*-oxides to dipolarophiles and hence allow for an increased yield of cycloaddition product. Initially, the cycloreversion reactions of various 3,4-disubstituted furoxans were investigated, with a view towards utilising the cycloreversion of furoxans as a general source of nitrile oxides. The tethering of nitrile oxides to a solid support in order to reduce the local concentration and thus reduce dimerisation was also investigated.



(**17**)



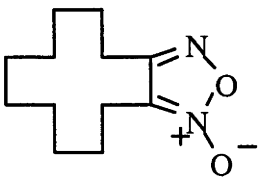
(**61**)

In addition, the cycloaddition chemistry of various analogues of both propanenitrile *N*-oxide (**17**) and 2-oxopropanenitrile *N*-oxide (**61**) was investigated. The nitrile oxides (**17**)[45, 46] and (**61**)[82] are reported as relatively short-lived species. Steric bulk is known to have an effect on dimerisation, as described in section 1.1. It was considered that by

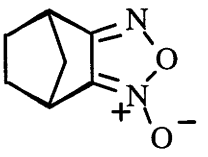
increasing the steric bulk of an alkylnitrile oxide, it would be possible to reduce its rate of dimerisation and hence allow for a greater extent of cycloaddition.

1.3.2 Cycloreversion

As a means of avoiding the problems engendered by the dimerisation of nitrile oxides, a preliminary investigation of the cycloreversion chemistry of furoxans was carried out. As discussed above, certain strained furoxans have been shown to undergo a cycloreversion at elevated temperatures to give two equivalents of the nitrile oxide. Generally, only furoxans possessing a high degree of steric strain undergo cycloreversion under conditions sufficiently mild to prevent rearrangement to isocyanates. For example, decamethylenefuroxan **(62)** undergoes cycloreversion at 261°C, followed by immediate rearrangement to decamethylene diisocyanate.[53] However, the heavily strained norbornenefuroxan **(63)** gives the *bis*-nitrile oxide **(64)** at 110°C, which can either 'dimerise' to give the polymeric furoxan **(65)**, or be trapped by a dipolarophile.[83]



(62)



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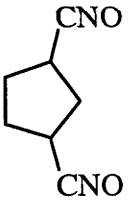

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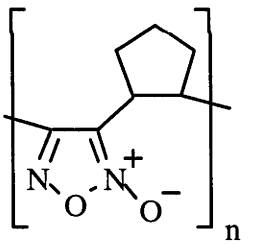
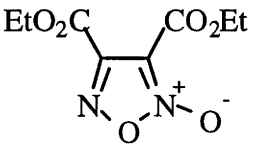


(65)



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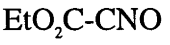
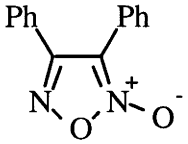


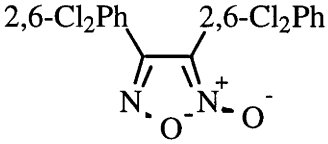
(67)

Two systems were investigated as part of this study. The first involved direct observation of 3,4-bis(ethoxycarbonyl)furoxan **(66)** by ^{1}H NMR spectroscopy. This was done in order to determine whether cycloreversion could be observed directly at high temperatures by observing a change in the resonance signals in the ^{1}H NMR spectrum. This system was chosen due to the relative clarity of the proton resonances in its ^{1}H NMR

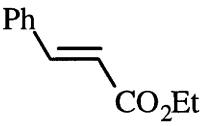
spectrum. Additionally, the conjugated nature of the resultant nitrile oxide (**67**) was expected to provide a degree of stability, facilitating its formation.



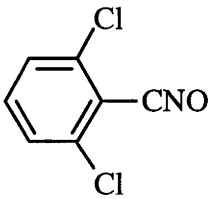
(**68**)



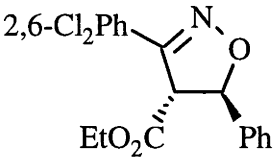
(**69**)



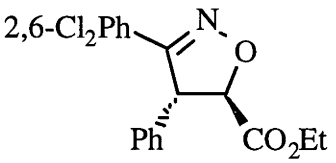
(**70**)



(**71**)



(**72**)

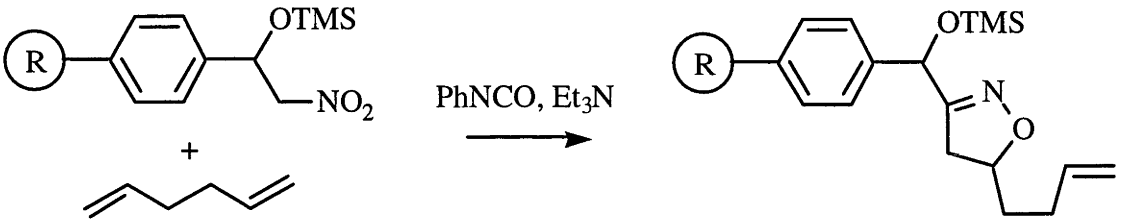


(**73**)

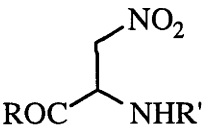
The other system investigated in this section was the cycloreversion of 3,4-diphenylfuroxan (**68**), and its analogue, 3,4-bis(2,6-dichlorobenzo)furoxan (**69**). The cycloreversion of 3,4-diphenylfuroxan (**68**) at high temperatures has been shown by the trapping of the nitrile oxide (**3**) using tetradec-1-ene as a solvent, at 245°C.[53] The present study was carried out in the presence of a different dipolarophile. This was done in order to study the effect of an increase in steric bulk on both the cycloreversion and the subsequent cycloaddition, in terms of extent of reaction with the dipolarophile and regiochemistry of the cycloaddition. Ethyl cinnamate (**70**) was chosen as a dipolarophile as both benzonitrile *N*-oxide (**3**)[74] and 2,6-dichlorobenzonitrile *N*-oxide (**71**)[84, 85] are known to react with cinnamic esters in order to form a mixture of regioisomeric isoxazolines. As described in section 1.2, methyl cinnamate (**45**) reacts with benzonitrile *N*-oxide (**3**) in ether at 35°C to give the regioisomers (**46**) and (**47**) in a ratio of 70:30. 2,6-Dichlorobenzonitrile *N*-oxide (**71**) reacts with ethyl cinnamate (**70**) in 30% aqueous ethanol solution at 37°C to give the regioisomeric isoxazolines (**72**) and (**73**) (Ar = 2,6-Cl_2Ph) in a ratio of 61:39. It should be noted that the nature of the solvent rarely seems to affect the regioisomer ratio.[9] The synthesis of precursors and the cycloreversion experiments are described in Chapter 2.

1.3.3 Solid Support

Solid support methods potentially offer a number of advantages for nitrile oxide cycloaddition. It was envisaged that tethering a nitrile oxide to a solid support would effectively limit the local concentration of nitrile oxide, preventing dimerisation. Beebe, Schore and Kurth[86] have performed 1,3-dipolar cycloaddition reactions using a polymer-supported nitrile oxide. Their procedure generates a nitrile oxide from a nitromethylbenzene derivative attached to a 2% crosslinked polystyrene/divinylbenzene resin using the Mukaiyama procedure (Scheme 10).



Scheme 10



(74)

It was intended that a system similar to that of Beebe, Schore and Kurth[86] could be used to generate alkylnitrile oxides on a solid support. The system chosen was based around ω-nitrocarboxylic acids, particularly amino acids such as the β-nitroalanine derivative (**74**). It was envisaged that such compounds could be tethered to a solid support through the carboxylate moiety, using solid-support peptide synthesis techniques.[76] A nitrile oxide would then be generated from this primary ω-nitrocarboxylic acid by dehydration using phenyl isocyanate and triethylamine (the Mukaiyama procedure). It was envisaged that using an amino acid nitrile oxide such as the nitroalanine derivative (**74**) would lead to a large range of 3-functionalised isoxazolines and β-functionalised amino acids. The advantage of using the Mukaiyama method over the halogenation method on a

solid support is that the conditions used to transform the molecule while it is attached to the support are milder and less likely to cause side reactions. The amino acid system was chosen in order to exploit the well-established solid-phase synthesis techniques in this area.[87] The synthesis of a model compound and an investigation of its cycloaddition chemistry are presented in Chapter 3.

1.3.4 Steric Auxiliaries

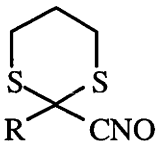
As described in section 1.1, the effect of steric bulk on the lifetime of aromatic nitrile oxides is well known. Less well documented is the effect of steric bulk on the lifetime of aliphatic nitrile oxides. The reduced extent of dimerisation in sterically hindered nitrile oxides can lead to an increase in the extent of cycloaddition to dipolarophiles. This is seen in the cycloaddition of nitrile oxides that are stable at room temperature such as mesitylnitrile oxide **(19)**[24] and adamantanecarbonitrile *N*-oxide **(22)**.[50] Similarly, 2,2-dimethylpropanenitrile *N*-oxide **(18)**, despite its stability towards dimerisation, adds rapidly to styrene ($t_{1/2} \approx 30$ min).[12]

(16) **(75)**

Zinner and Günther[46] describe the rapid dimerisation at room temperature of ethanenitrile *N*-oxide **(16)** and 2-ethylbutanenitrile *N*-oxide **(75)**. These nitrile oxides were generated and isolated at *ca.* –15°C, and were found to dimerise rapidly at room temperature.[88] Mitchell and Paton[51] have formed ethanenitrile *N*-oxide **(16)** from the thermal fragmentation of 2,3-dimethylfuroxan using flash vacuum pyrolysis. The nitrile oxide was prevented from reforming the furoxan by maintaining the cold trap temperature at less than -40°C. On warming to room temperature, the dimerisation was monitored by ^{1}H and ^{13}C NMR spectroscopy. While generally reported as being immeasurably fast,[4, 9, 45]

complete dimerisation of ethanenitrile *N*-oxide (**16**) took three days in solution. The bulkier analogue, 2,2-dimethylpropanenitrile *N*-oxide (**18**), took longer than one month to completely dimerise under similar conditions.[12]

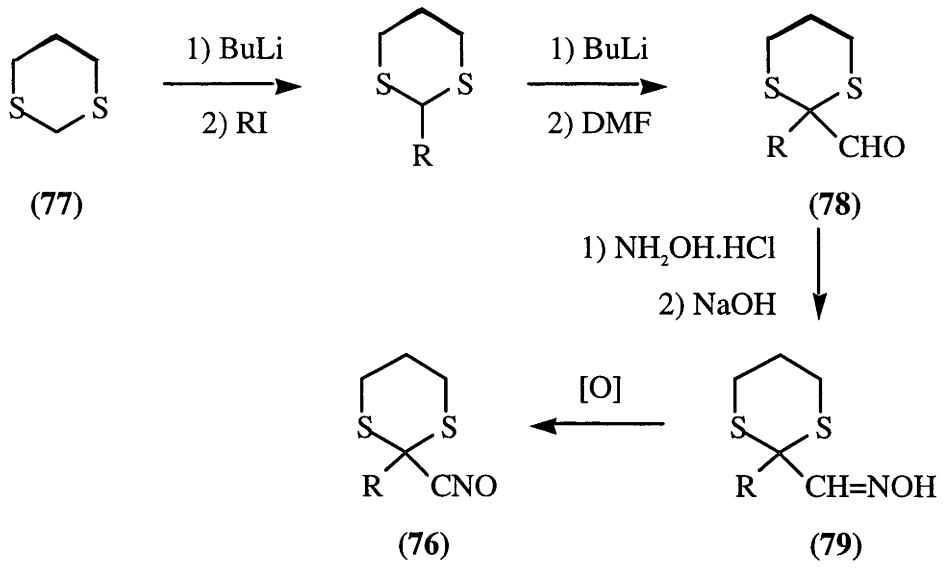
It was considered that the lifetime of aliphatic nitrile oxides could be extended by increasing their steric bulk, in a manner directly analogous to that seen for aromatic nitrile oxides. Further, by the use of a removable protecting group, direct analogues of the cycloaddition products of simple aliphatic nitrile oxides could be generated, allowing the synthesis of isoxazolines not readily available *via* more common nitrile oxide generation techniques.



(76)

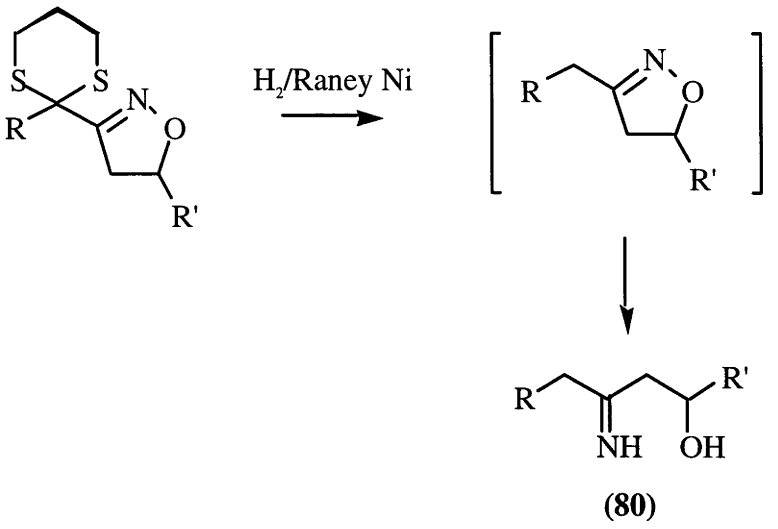
The system chosen was the 1,3-dithiane-2-carbonitrile *N*-oxide framework of the type (**76**), and variations thereof. The stability of these compounds was expected to be similar to that of the known tertiary nitrile oxides 2,2-dimethylpropanenitrile *N*-oxide (**18**), which has a lifetime of several days (neat),[88] and adamantanecarbonitrile *N*-oxide (**22**), which is reported as being indefinitely stable at room temperature.[50] This level of stability was expected as a result of the similar steric requirements of the nitrile oxide side chain.

The proposed synthetic scheme, described in Scheme 11, involved the alkylation and formylation of 1,3-dithiane (**77**) to give 2-alkyl-1,3-dithiane-2-carboxaldehydes (**78**).[89, 90] These aldehydes were to be transformed into oximes (**79**),[22] from which the nitrile oxides (**76**) would be generated. The lithiation protocol was chosen due to its adaptability. A wide range of 2-substituted-1,3-dithianes have previously been synthesised using this procedure.[90, 91]



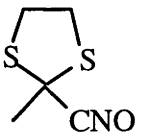
Scheme 11

The dithiane moiety was considered desirable due to its relative ease of removal. The 1,3-dithiane moiety can be removed either using hydrolysis (oxidative or otherwise) to afford a carbonyl group,[92-98] or using reduction which results in a methylene group.[98-100] In this way, the nitrile oxides **(76)** can be considered analogues of the nitrile oxides **(17)** and **(61)** and their longer-chain counterparts. Isoxazolines can be ring-opened to β-hydroxy ketones **(80)** using Raney nickel.[101, 102] This reagent will also remove a dithiane moiety.[98-100] To take advantage of this, the combined deprotection and ring-opening procedure shown in Scheme 12 was proposed, allowing both transformations to be carried out in one step.



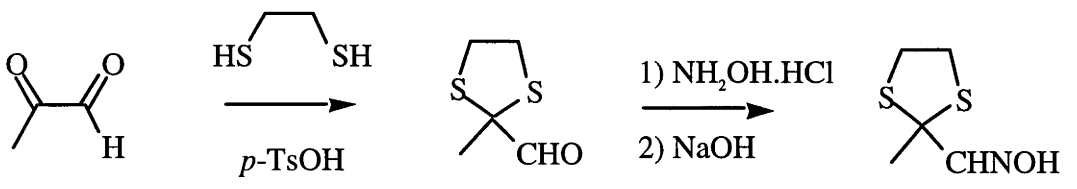
(80)

Scheme 12



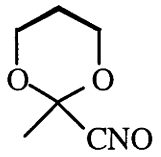
(81)

As well as the dithiane systems, the synthesis and cycloadditions of the dithiolanenitrile oxide **(81)** were also considered to be of interest. This nitrile oxide was synthesised in order to examine the effect of a small change of steric bulk on the system; the 5-membered dithiolane ring was considered to possess less steric bulk than the six-membered dithiane ring due to the increased ring-strain. The proposed synthesis of this species is shown in Scheme 13. The aldehyde **(83)** can be synthesised readily from pyruvaldehyde **(82)** and 1,3-propanedithiol.[103] This aldehyde **(83)** would then be converted to the oxime **(84)** by standard methods.[22]

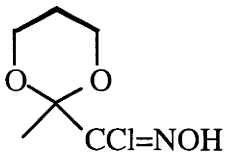


(82) **(83)** **(84)**

Scheme 13



(85)

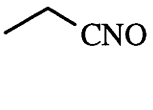


(86)

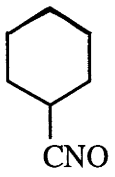
The synthesis of a dioxane analogue **(85)** of the dithianenitrile oxides **(76)** *via* a number of routes was also investigated. This species was expected to have different steric and electronic properties to those of the dithiane system **(76)**, and was desired in order to determine the effect on the cycloaddition reaction of the dioxane moiety compared to the dithiane moiety of the nitrile oxides **(76)**. In addition, the lower reactivity of the dioxane moiety towards oxidation was expected to allow the synthesis of the hydroximinoyl chloride precursor **(86)**. This was considered advantageous as the nitrile oxide **(85)** could then be generated quantitatively from the hydroximinoyl chloride **(86)**, simplifying the analysis of the cycloaddition reactions. However, the analogues of cycloadducts of propanenitrile *N*-oxide **(17)** are less readily accessible from the cycloadducts of the dioxanenitrile oxide **(85)**, as the dioxane unit cannot be removed directly by reduction. Analogues of the cycloadducts of 2-oxopropanenitrile *N*-oxide **(61)** were thought to be available *via* hydrolysis.

The alkylnitrile oxides propanenitrile *N*-oxide **(17)**, cyclohexanecarbonitrile *N*-oxide **(87)** and adamantanenitrile *N*-oxide **(22)** were synthesised, as was 2-oxopropanenitrile *N*-oxide **(61)**, as control compounds for the comparison of nitrile oxide stability, reactivity and regioselectivity. These nitrile oxides were examined in order to determine the effect of the electronic and steric effects of the heteroatoms present in the nitrile oxides **(76)**, **(81)** and **(85)** on their stability and cycloadditions. The proposed synthesis of the alkylnitrile oxides **(17)**, **(87)** and **(22)** involved elimination of the corresponding hydroximinoyl chlorides, which were synthesised according to standard methods from their parent aldehydes.[22] 2-Oxopropanenitrile *N*-oxide **(61)** was also to be

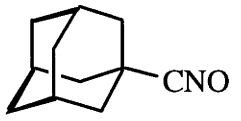
generated from the corresponding hydroximinoyl chloride; this hydroximinoyl chloride was to be synthesised by nitronation of chloroacetone.[104]



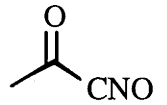
(17)



(87)



(22)



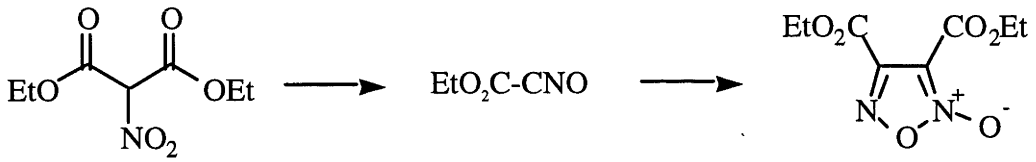
(61)

The syntheses of the oxime precursors to the nitrile oxides studied are described in Chapter 4. The subsequent generation of the nitrile oxides from these precursors and an examination of their properties are presented in Chapter 5. An investigation of the synthetic utility of these nitrile oxides, including the effect of the various steric auxiliaries on the extent and regiochemical course of cycloaddition is presented in Chapter 6. An examination of the deprotection of the dithiane series is also presented in Chapter 7.

Chapter 2: Results and Discussion - Cycloreversion of Furoxans

2.1 3,4-Bis(ethoxycarbonyl)furoxan

As discussed in the introduction, as a means of avoiding the problems engendered by the dimerisation of nitrile oxides, the cycloreversion chemistry of furazan *N*-oxides (furoxans **(11)**) was investigated. To this end, 3,4-bis(ethoxycarbonyl)furoxan **(66)** was synthesised as a model of furoxan behaviour at high temperatures. Diethyl α-nitromalonate **(88)** is readily thermolysed to give the nitrile oxide **(67)**, which dimerises rapidly in the absence of a dipolarophile to give the furoxan **(66)** (Scheme 14). The furoxan **(66)** was isolated by distillation, albeit in a low yield.



(88) **(67)** **(66)**

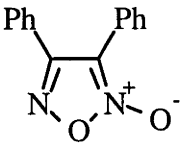
Scheme 14

The ^{1}H NMR spectrum of the furoxan **(66)** (300 MHz, d_8-toluene) consists of two overlapping triplet signals at δ0.89 and δ0.94 (integration 6H total), and two quartet signals at δ3.84 and δ3.95 (relative integration 2H each). This spectrum clearly shows the non-equivalence of the ethoxy groups in the 3- and 4-positions. It was expected that the nitrile oxide **(67)** would show a pattern of ^{1}H NMR signals consistent with a single ethyl ester. If cycloreversion was observed, the ^{1}H NMR spectrum would therefore be expected to show either a distinct resonance for the nitrile oxide **(67)**, or a signal averaged between those of the nitrile oxide **(67)** and of the furoxan **(66)** if cycloreversion is rapid.

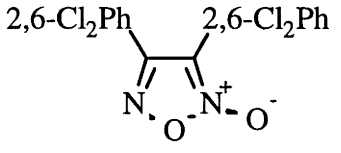
3,4-Bis(ethoxycarbonyl)furoxan **(66)** was heated from room temperature to 92 C in d_8-toluene and its ^{1}H NMR spectrum was observed at intervals over this temperature range in order to determine its propensity for cycloreversion. The ^{1}H NMR spectrum was recorded at 25 C, 47 C, 70 C and 92 C. A broadening of the ^{1}H NMR signal was observed,

which occurred slightly at 70 C and in a more pronounced fashion at 92 C. Although this observation is consistent with the expected spectrum if cycloreversion were to occur, the change is too slight to allow definitive identification of a species such as the nitrile oxide (**67**). For this reason the cycloreversion of other furoxans at higher temperatures was investigated.

2.2 3,4-Diarylfuroxans



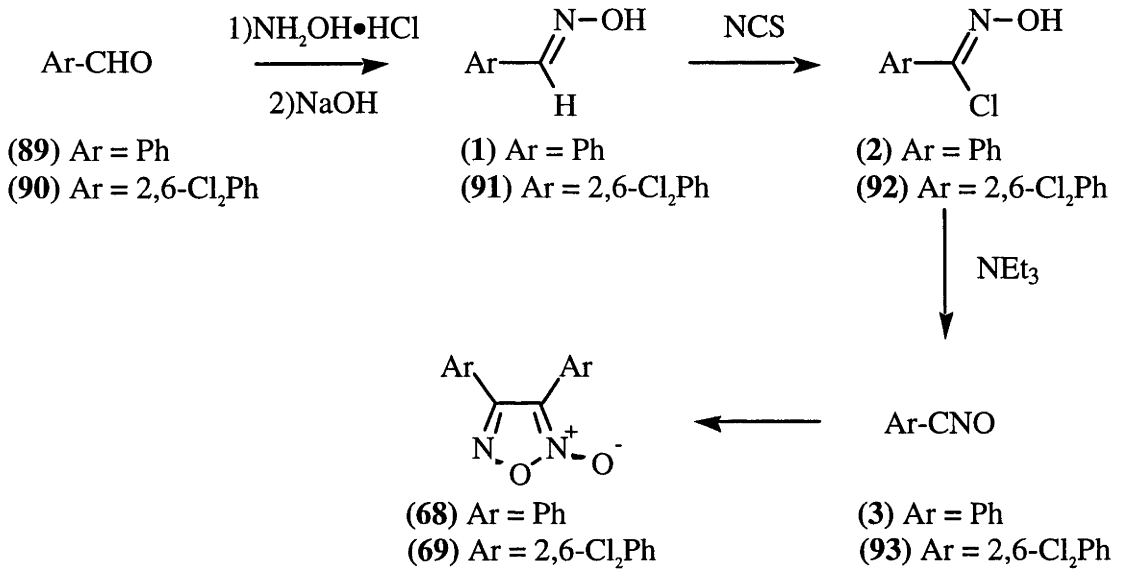
(**68**)



(**69**)

The behaviour of 3,4-diphenylfuroxan (**68**) and 3,4-bis(2,6-dichlorobenzo)furoxan (**69**) was considered. 3,4-Bis(ethoxycarbonyl)furoxan (**66**) was not used in these studies as it undergoes 1,3-dipolar cycloaddition as a nitrone in preference to cycloreversion at high temperatures.[105] The steric bulk of the furoxans (**68**) and (**69**) was expected to facilitate cycloreversion. 3,4-Diphenylfuroxan (**68**) has been shown to revert at high temperatures.[51, 53] The furoxans (**68**) and (**69**) were synthesised by direct dimerisation of the corresponding nitrile oxides (**3**) and (**93**). In order to synthesise the nitrile oxides (**3**) and (**93**), the corresponding aldehydes (**89**) and (**90**) were treated with hydroxylamine hydrochloride in a basic ethanol/water solution to form the oximes (**1**) and (**91**) respectively. The oximes (**1**) and (**91**) were chlorinated using *N*-chlorosuccinimide in DMF to give the hydroximinoyl chlorides (**2**) and (**92**) respectively.[22] The hydroximinoyl chlorides (**2**) and (**92**) were treated with triethylamine in THF to give the nitrile oxides (**3**) and (**93**) by elimination of hydrogen chloride. The neat nitrile oxide (**3**) dimerises to the furoxan (**68**) over the course of several hours, while the neat nitrile oxide (**93**) dimerises to the furoxan (**69**) over several weeks (Scheme 15). The time allowed for dimerisation was in accordance with the lifetimes assigned to the nitrile oxides (**3**) and (**93**) in the literature.[48, 88] The ^{1}H NMR spectra of the furoxans (**68**) and (**69**) are of limited use in

confirming their structure. The furoxans (**68**) and (**69**) were therefore identified using mass spectroscopy. The mass spectrum of the furoxan (**68**) shows a molecular ion at *m/z* 238. The base peak at *m/z* 178 represents the fragment $[M - N_2O_2]^{+}$, a common fragmentation of furoxans.[60, 106] The mass spectrum of the furoxan (**69**) gives a predominant molecular ion at *m/z* 376. The isotope pattern indicates four chlorine atoms. The base peak at *m/z* 316 represents the fragment $[M - N_2O_2]^{+}$.



(**89**) Ar = Ph
(**90**) Ar = 2,6-Cl_2Ph

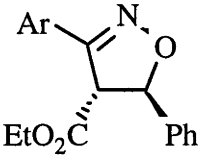
(**1**) Ar = Ph
(**91**) Ar = 2,6-Cl_2Ph

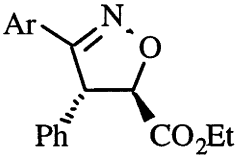
(**2**) Ar = Ph
(**92**) Ar = 2,6-Cl_2Ph

(**3**) Ar = Ph
(**93**) Ar = 2,6-Cl_2Ph

(**68**) Ar = Ph
(**69**) Ar = 2,6-Cl_2Ph

Scheme 15





(**72a**) Ar = Ph
(**72b**) Ar = 2,6-Cl_2Ph

(**73a**) Ar = Ph
(**73b**) Ar = 2,6-Cl_2Ph

Initially, the furoxans (**68**) and (**69**) were treated with ethyl cinnamate (**70**) at room temperature in THF as a control experiment, to see if any cycloaddition or other reaction takes place. No reaction was observed, which was as expected.

The procedure was repeated at higher temperatures in order to determine if the reaction could be 'forced' under more extreme conditions. The furoxans (**68**) and (**69**)

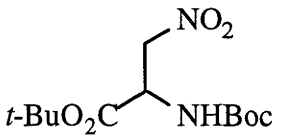
were dissolved in 1,2,4-trimethylbenzene (bp 168 C) in the presence of ethyl cinnamate (**70**) and the mixtures were heated at reflux. After several days at reflux, the solvent was removed from each reaction mixture under reduced pressure and the residues were analysed by ^{1}H NMR spectroscopy. No cycloaddition product was observed in the case of 3,4-diphenylfuroxan (**68**). This suggests that cycloreversion does not take place at this temperature. In the case of 3,4-bis(2,6-dichlorobenzo)furoxan (**69**), however, the ^{1}H NMR spectrum of the crude reaction mixture showed traces of a number of signals corresponding to the adducts (**72b**) and (**73b**). The characteristic isoxazoline signals are doublets at δ6.24 and δ4.57 for the isoxazoline (**72b**), and doublets at δ5.28 and δ5.25 for the isoxazoline (**73b**).[84] The ^{1}H NMR spectrum also showed a large proportion of other signals, representing residual solvent and presumed decomposition products. The largest of these signals are two large multiplets spanning the regions δ6.9-7.7 and δ2.1-2.4. The low-field multiplet covers the region expected to contain the aromatic resonances in the product. The intensity of the signals at δ5.28 and δ4.57 was measured relative to that of an internal standard, *t*-butyl methyl ether, (δ3.2, s, 3H). This indicated a yield of approximately 10-25%. Due to a poor signal to noise ratio, it was not possible to determine the yield more precisely.

The procedure was repeated in 1,2,4-trichlorobenzene (bp 214 C). After 4 days at this temperature both 3,4-diphenylfuroxan (**68**) and 3,4-bis(2,6-dichlorobenzo)furoxan (**69**) showed signs of cycloreversion. The furoxan (**68**) gave a mixture of products, including the cycloadduct (**72a**). The presence of this isomer was indicated by signals in the ^{1}H NMR spectrum of the crude reaction product at δ5.99 (d) and δ4.46 (d), which are characteristic of the isoxazoline (**72a**).[107, 108] The yield of the isoxazoline (**72a**) was calculated at less than 10% by comparison of the intensities of the isoxazoline resonances to those of the methyl ether resonance of the internal standard, *t*-butyl methyl ether, and the cycloadduct (**73a**) was not observed. 3,4-Bis(2,6-dichlorobenzo)furoxan (**69**) also reacted at 214 C to give only one regioisomer, the 5-phenylisoxazoline (**72b**), which was identified

by characteristic signals in its ^{1}H NMR spectrum at δ6.24 (d) and δ4.57 (d). The yield of the isoxazoline **(72b)** as determined by comparison of integration of signals in the ^{1}H NMR spectra with those of an internal standard (*t*-butyl methyl ether) was less than 10%. The reason for the apparent increase in regioselectivity that was observed in the 3,4-bis(2,6-dichlorobenzo)furoxan **(69)** system at the higher temperature is unclear. It is possible that the increase in energy of the system allows the cycloreversion of the isoxazoline **(73b)**, resulting in a preference for the isomer **(72b)**. Large amounts of other products were also observed in each experiment. It is possible that these byproducts result from thermal decomposition of ethyl cinnamate **(70)** and the isoxazolines **(72)** and **(73)**. More efficient trapping of the nitrile oxides formed by thermal decomposition of furoxans might be possible with more stable dipolarophiles, such as alkyl-substituted alkenes. However, this would severely limit the potential of the resultant isoxazolines for elaboration, which suggests that an alternative methodology would be desirable.

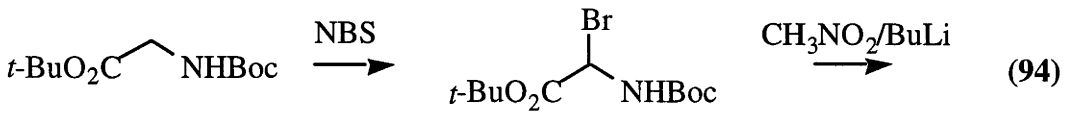
Chapter 3: Results and Discussion - Preliminary Studies Toward Polymer Supported Nitrile Oxides

As described in section 1.3.3, the synthesis of an alkylnitrile oxide attached to a solid support through a carboxylate group was proposed. It was considered desirable to synthesise a model compound prior to the investigation of solid support chemistry. To this end, the protected alanine derivative, *N*-boc-β-nitroalanine *t*-butyl ester (**94**) was synthesised.



(**94**)

N-Boc-β-nitroalanine *t*-butyl ester (**94**) was synthesised from *N*-boc-glycine *t*-butyl ester (**95**) as described in Scheme 16.[109] *N*-Boc-glycine *t*-butyl ester (**95**), prepared by esterification of *N*-boc-glycine was brominated using *N*-bromosuccinimide to form the protected α-bromoglycine (**96**), which was used without purification. The α-bromoglycine derivative (**96**) was treated with nitromethane anion generated by treatment of nitromethane with butyllithium to give the protected nitroalanine (**94**). This product was identified using its ^{1}H NMR spectrum. A multiplet at δ4.5-δ4.6 represents the α-proton, while the prochiral β-protons give rise to separate doublets of doublets signals at δ4.78 (1H) and δ4.92 (1H).



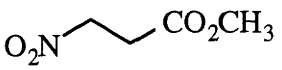
(**95**) (**96**) (**94**)

Scheme 16

The β-nitroalanine derivative (**94**) was treated with phenyl isocyanate and a catalytic amount of triethylamine in order to generate a nitrile oxide.[35] Methyl acrylate (**34**)

was present as a dipolarophile. The ^{1}H NMR spectroscopic evidence suggests that no reaction occurred, as only starting materials were observed. Since methyl acrylate **(34)** is known to have a high reactivity towards dipoles,[70] the lack of cycloaddition products suggested that the desired nitrile oxide was not being formed.

The nitroalanine derivative **(94)** is also unreactive in nitroaldol reactions.[110] The generation of a nitrile oxide from a primary nitroalkane is known to proceed *via* a nitronate anion, which attacks phenyl isocyanate in a nucleophilic manner.[35] As both the nitroaldol and the Mukaiyama reactions proceed *via* a nitronate anion, it was considered likely that the reason for the lack of reactivity of the molecule **(94)** in the Mukaiyama reaction was due to a decrease in nucleophilic activity of this anion. It was considered that the lack of nucleophilic reactivity of this anion might be due to steric interference from the bulky amino acid protecting groups.

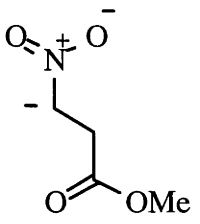


(97)

The β-nitroester **(97)** was thought to serve as a further simplified model compound; it has less steric bulk than the amino-acid derivative **(94)**, however it still retains sufficient functionality to allow attachment to a solid-support through the carboxylic acid moiety. Methyl 3-nitropropanoate **(97)** was treated with phenyl isocyanate and triethylamine in the presence of methyl acrylate **(34)**. No reaction was observed. This indicates that the ester moiety has a significant negative effect on the reactivity of the amino acid derivative **(94)** towards dehydration.

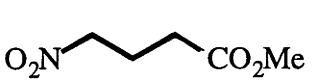
The possibility that anion formation at C2 (α to the carbonyl group) rather than C3 (α to the nitro group) is responsible for the lack of reactivity of the nitro-acids **(94)** and **(97)** can be discounted by comparing the standard pK_a values of the relevant protons. A proton attached to a carbon adjacent to an ester has a pK_a of approximately 24 whereas a proton

attached to a carbon adjacent to a nitro group has a pK_a of approximately 10.[111] Additionally, anion formation on C-2 results in elimination of the nitro-group.[112]



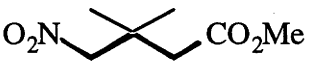
(98)

Although considered slight, there was a possibility that an inductive electron withdrawing effect from the ester group was reducing the nucleophilicity of the nitronate anion (**98**). In order to investigate this theory, the reaction of commercially available methyl 4-nitrobutanoate (**99**) was investigated. The nitro group in the γ-nitroester (**99**) was considered remote enough that any inductive effect would be negligible. However, the nitroester (**99**) was also found to be unreactive under Mukaiyama conditions.



(99)

(100)



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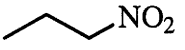

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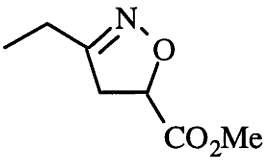


(103)

The lack of reactivity of the ω-nitroesters (**97**) and (**99**) under Mukaiyama conditions is surprising given that literature precedent exists for the generation of nitrile oxides from methyl γ-nitrobutanoate (**99**)[113-115] as well as from compounds similar to those examined, methyl 2,2-dimethyl-3-nitropropanoate(**100**)[116, 117] and methyl 3,3-dimethyl-4-nitrobutanoate (**101**).[113, 114, 117] However, no reaction of either of the ω-nitroesters (**97**) or (**99**) was observed in toluene at room temperature or at 80 C, or in THF. The

effectiveness of the conditions used was confirmed by the generation of the nitrile oxide (**17**) from 1-nitropropane (**102**). The presence of the nitrile oxide (**17**) was confirmed by trapping with methyl acrylate (**34**), yielding methyl 3-ethyl-4,5-dihydroisoxazole-5-carboxylate (**103**). This compound was identified using its ^{1}H NMR spectrum; characteristic isoxazoline resonances are visible at δ5.01 (1H, t, J = 9 Hz) and δ3.24 (2H, d, J = 9 Hz).

A possible explanation for the observed lack of reactivity of the γ-nitroester (**97**) is that it may adopt a *pseudo*-five-membered ring conformation through intramolecular electrostatic forces. This conformation is depicted in Figure 4. The small change in electronic character of the nitro-group may then be sufficient to prevent nucleophilic attack of the nitro-oxygen to phenyl isocyanate, arresting the reaction at this step. The amino acid derivative (**94**) could possibly adopt a similar conformation, while the nitroester (**99**) could possibly adopt a *pseudo*-six-membered ring conformation, preventing the reaction of these compounds. The formation of such a conformation may also explain the observation that the β-nitroalanine derivatives are unreactive in nitroaldol reactions.

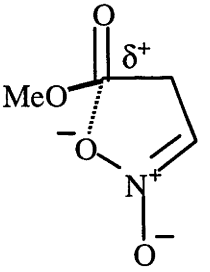


Figure 4: Proposed conformation adopted by methyl γ-nitropropanoate.

Due to the lack of reactivity of the test compounds, the solid support experiments were not carried out. A recent publication[118] details the synthesis of a solid-supported analogue of benzohydroximinoyl chloride (**2**) and its utility in cycloaddition reactions. An alternative procedure for the generation of a solid supported amino acid nitrile oxide using a similar approach was considered, involving the oxidation of an N,C-protected serine derivative to give a glycine α-carboxaldehyde, followed by oxime formation and

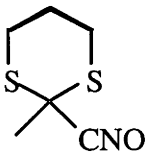
chlorination to give the nitrile oxide precursor, the hydroximinoyl chloride. However, this procedure was deemed impractical for this aspect of the project, as it would too severely limit the range of peptides available for this technique due to the relatively harsh procedures necessary.

Chapter 4: Results and Discussion - Synthesis of Precursors to Sterically Hindered Nitrile Oxides

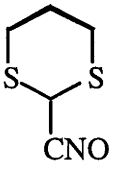
As neither cycloreversion nor the solid support chemistry appeared to provide useful methods of alleviating the dimerisation of nitrile oxides, a third method was investigated. This involved the synthesis of nitrile oxides possessing large steric bulk, in an effort to determine the effect of this added bulk on dimerisation.

As discussed in the introduction, nitrile oxides may be synthesised from a variety of precursors. Most of the nitrile oxides that were investigated in this study were synthesised from their corresponding oximes by either chlorination followed by elimination or by direct oxidation. This chapter discusses the synthesis of the oximes as the common precursors in the nitrile oxide syntheses.

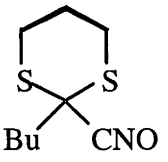
4.1 1,3-Dithiane-2-carboxaldehyde Oximes



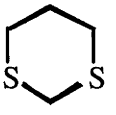
(104)



(105)



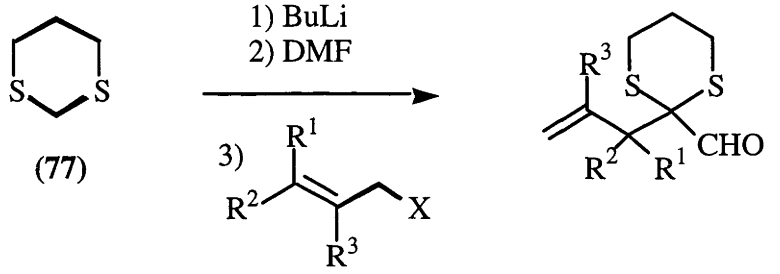
(106)



(77)

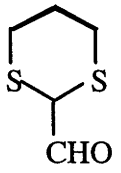
2-Methyl-1,3-dithiane-2-carbonitrile *N*-oxide **(104)** was synthesised in order to determine the effect of the steric bulk of a nitrile oxide on its dimerisation. The rate of dimerisation was to be compared with that of smaller nitrile oxides such as propanenitrile *N*-oxide **(17)** and 2-oxopropanenitrile *N*-oxide **(61)**. The synthesis of 1,3-dithiane-2-carbonitrile *N*-oxide **(105)** was also investigated as a species with intermediate steric bulk for comparison purposes. In addition, 2-butyl-1,3-dithiane-2-carbonitrile *N*-oxide **(106)** was synthesised in order to demonstrate the generality of the synthetic procedure. Each of these nitrile oxides was to be synthesised from the corresponding oxime.

The desired oximes were synthesised *via* the 2-lithioanion of 1,3-dithiane (**77**). Wilson and Mathew[119] have successfully used a 1,3-dithiane lithiation procedure in the one-pot synthesis of 2-allyl-1,3-dithiane-2-carboxaldehydes (Scheme 17). The reaction proceeds *via* the intermediate 1,3-dithiane-2-carboxaldehyde (**107**), formed by nucleophilic attack of the 1,3-dithiane anion on *N,N*-dimethylformamide (DMF). The aldehyde (**107**) is acidic, and deprotonates in the presence of dimethylamine anion to give an anion, which attacks the electrophile in a nucleophilic manner to give a 2-allyl-1,3-dithiane-2-carboxaldehyde of the type illustrated in Scheme 17.

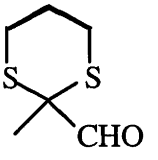


(77)

Scheme 17



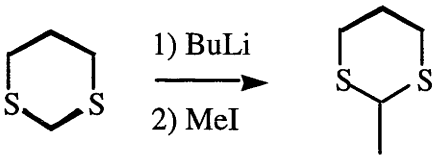
(107)



(108)

The synthesis of 2-methyl-1,3-dithiane-2-carboxaldehyde (**108**) was attempted in a similar manner. Initially, the procedure was attempted in one pot. 1,3-Dithiane (**77**) was treated with butyllithium in THF at -30°C to give the 2-lithio-anion. DMF was added in a dropwise manner and the reaction mixture was stirred at 4°C overnight. Methyl iodide was then added to the reaction mixture. ^{1}H NMR spectroscopy of the crude product mixture showed a complex mixture of products. 2-Methyl-1,3-dithiane-2-carboxaldehyde (**108**) was barely detectable, with the aldehyde signal visible as a trace resonance at δ9.05. It was thought that the poor formation of the desired product (**108**) was due to homoaldol

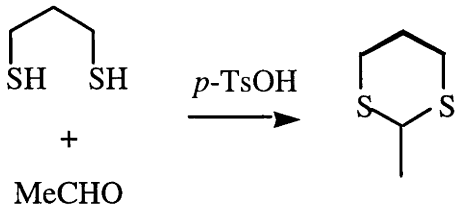
reactions of the 1,3-dithiane-2-carboxaldehyde anion proceeding in preference to nucleophilic attack of the anion on methyl iodide. For this reason, the synthesis was carried out in a stepwise manner, rather than in one pot, according to the procedure of Still and Strautmanis,[120] a modification of the alkylation chemistry presented by Seebach and Corey.[90] 1,3-Dithiane (**77**) was alkylated first (Scheme 18), prior to formylation in a separate procedure.



(77) **(109)**

Scheme 18

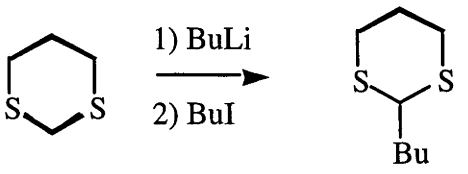
1,3-Dithiane (**77**) was treated with butyllithium to form an anion. In order to monitor formation of the anion, an aliquot of the reaction mixture was quenched in D_2O. The extent of anion formation was determined by observing the relative strength of the proton signal at δ3.72 in the NMR spectrum of the aliquot. This singlet represents the acidic C2 protons. A relative integration of 2 protons represents no deprotonation, while a relative integration of 1 proton represents complete anion formation. It was necessary to use more than one equivalent of butyllithium as anion formation was slow and was usually incomplete after several hours at -20°C. Best results were observed with 2 equivalents of base; anion formation was complete after 4 hours at -20°C - -10°C. Methyl iodide was added to the solution containing the anion and the reaction mixture was stirred for several hours. ^{1}H NMR spectroscopy of the crude reaction mixture shows a mixture of 1,3-dithiane (**77**) (2H singlet at δ3.72, C2-H_2) and 2-methyl-1,3-dithiane (**109**) (1H quartet at δ4.13, C2-H, 3H doublet at δ1.5, -CH_3). 2-Methyl-1,3-dithiane (**109**) was purified by distillation, in an overall yield of 40-50%.



(109)

Scheme 19

2-Methyl-1,3-dithiane **(109)** was also synthesised by thioacetalisation of acetaldehyde (Scheme 19). A mixture of acetaldehyde and 1,3-propanedithiol was treated with gaseous hydrochloric acid. This procedure gives 2-methyl-1,3-dithiane **(109)** in 52% yield after distillation, although it is possible that the reaction did not go to completion. Both methods were satisfactory for the synthesis of 2-methyl-1,3-dithiane **(109)**. The alkylation method (Scheme 18) is considered to have the advantage of being more general for the synthesis of 2-substituted-1,3-dithianes, since the 2-substituent can easily be modified by varying the electrophile. The second method has the advantage of being a relatively simple procedure, but the range of compounds available for reaction is restricted to stable aldehydes.

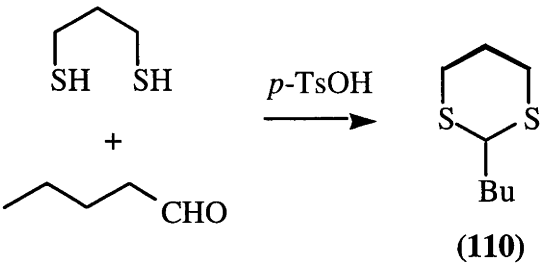


(77) **(110)**

Scheme 20

2-Butyl-1,3-dithiane **(110)** was synthesised (Scheme 20) from 1,3-dithiane **(77)**. 1,3-Dithiane **(77)** in THF was treated with butyllithium to form the corresponding lithio-anion. The formation of this anion was observed according to the D_2O quenching procedure described above. The anion was then treated with 1-iodobutane. The resultant compound, 2-butyl-1,3-dithiane **(110)** was purified by distillation and obtained in 34%

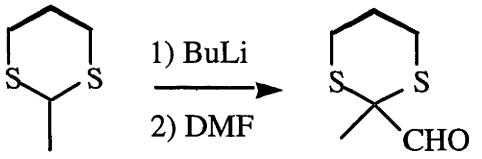
yield. This product was identified using the ^{1}H NMR signal for the C2 proton at δ4.05 (triplet, 1H).



(110)

Scheme 21

2-Butyl-1,3-dithiane **(110)** was also synthesised by treatment of valeraldehyde with 1,3-propanedithiol in the presence of *p*-toluenesulfonic acid at reflux in benzene (Scheme 21). Water was removed by means of a Dean-Stark apparatus. This procedure gave 2-butyl-1,3-dithiane **(110)** in 28% yield after distillation. Neither synthetic method gave a clear advantage over the other in the synthesis of 2-butyl-1,3-dithiane **(110)**.

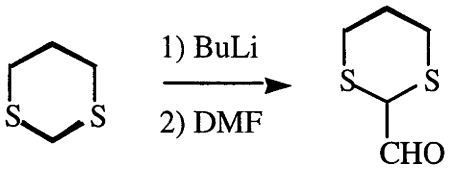


(109) **(108)**

Scheme 22

In order to synthesise 2-methyl-1,3-dithiane-2-carboxaldehyde **(108)**, 2-methyl-1,3-dithiane **(109)** was treated with butyllithium to form the corresponding 2-anion. Anion formation was monitored by quenching an aliquot of the reaction mixture with D_2O as described above. The ^{1}H NMR spectrum was observed. Incorporation of deuterium in the 2-position of 2-methyl-1,3-dithiane **(109)** from the quenching of the anion resulted in the disappearance of the resonance at δ4.1 and the loss of coupling in the resonance at δ1.5. Thus, the extent of anion formation could be determined by the intensity of the signal at δ4.1 in the ^{1}H NMR spectrum of the D_2O quenched aliquot. DMF (4 eq.) was added to the anion solution once anion formation was complete, to give 2-methyl-1,3-dithiane-

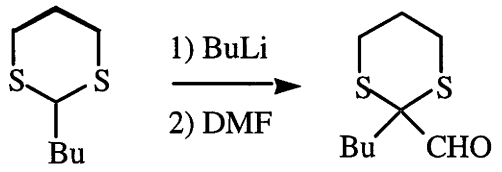
2-carboxaldehyde (**108**) in 32% yield (Scheme 22) from 1,3-dithiane (**77**). This compound was identified using the presence of an aldehyde resonance at δ9.04 (singlet, 1H) in its ^{1}H NMR spectrum.



(**77**) (**107**)

Scheme 23

Despite the difficulties with the one-pot synthesis of 2-methyl-1,3-dithiane-2-carboxaldehyde (**108**) from 1,3-dithiane (**77**), 1,3-dithiane-2-carboxaldehyde (**107**) was readily synthesised from 1,3-dithiane (**77**). 1,3-Dithiane (**77**) was treated with butyllithium followed by DMF as described above and the reaction mixture was quenched with water to give 1,3-dithiane-2-carboxaldehyde (**107**). The reaction mixture was acidified to below pH 6 and then extracted with ether, to give the aldehyde (**107**) in 44% yield (Scheme 23). 1,3-Dithiane-2-carboxaldehyde (**107**) is quite acidic and dissolves readily in the basic aqueous medium of the quenched reaction mixture, necessitating the acidic workup. The ^{1}H NMR spectrum of the aldehyde (**107**) shows resonances at δ9.53 and δ4.11, corresponding to the aldehyde and C2-protons respectively. These signals were slightly broadened, masking the expected coupling of 2 Hz described in the literature.[121]

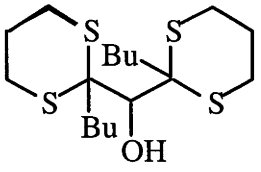


(**110**) (**111**)

Scheme 24

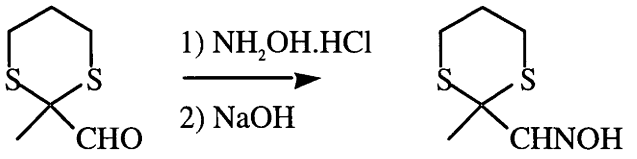
2-Butyl-1,3-dithiane-2-carboxaldehyde (**111**) was synthesised in an analogous manner to that described for the synthesis of 2-methyl-1,3-dithiane-2-carboxaldehyde (**108**). 2-Butyl-1,3-dithiane (**110**) was treated with butyllithium to form the

2-lithio-anion. The extent of anion formation was judged by the quenching of an aliquot with D_2O as described above and monitoring the intensity of the C2-proton signal at δ4.05 (t). It was found that adding DMF to a solution containing 2-butyl-2-lithio-1,3-dithiane as described by Meyer and Seebach[122] did not result in formation of 2-butyl-1,3-dithiane-2-carboxaldehyde (**111**). ^{1}H NMR spectroscopy of the product mixture showed a complex mixture of compounds, with a small signal at δ9.0 indicating some slight formation of the desired aldehyde (**111**). However, when a THF solution of 2-butyl-2-lithio-1,3-dithiane was added to a THF solution of DMF according to the general guidelines for 2-lithio-1,3-dithiane additions presented by Seebach and Corey,[90] the reaction proceeded. This gave 2-butyl-1,3-dithiane-2-carboxaldehyde (**111**) (Scheme 24) in a crude yield of 87%, which was used without further purification. The ^{1}H NMR spectrum of the aldehyde (**111**) shows a characteristic aldehyde resonance at δ9.03 (singlet, 1H). The reason for the difference in reactivity of the 2-lithio-anion of the butyldithiane (**110**) depending on the mode of introduction to DMF is unclear. It has been suggested[90] that in such reactions the resultant 1,3-dithiane-2-carboxaldehyde is susceptible to further nucleophilic attack from the 2-lithio-1,3-dithiane anion remaining in solution. In this case, this attack would result in the formation of a compound of structure (**112**). This necessitates the addition of the dithiane-anion to a large excess of formylating agent, in order to reduce the local concentration of the 1,3-dithiane-2-carboxaldehyde.



(112)

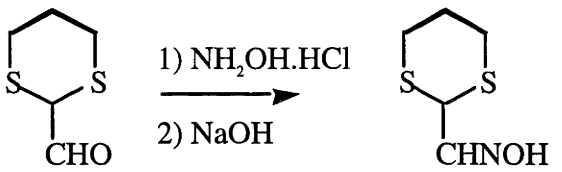
In order to synthesise 2-methyl-1,3-dithiane-2-carboxaldehyde oxime (**113**), 2-methyl-1,3-dithiane-2-carboxaldehyde (**108**) was treated with hydroxylamine hydrochloride in a basic solution of ethanol and water according to the method of Lui *et al.*[22] (Scheme 25). The reaction mixture was washed with ether before being acidified to



(108) **(113)**

Scheme 25

precipitate the oxime **(113)** from the basic solution. The precipitate was then extracted into ether. The oxime **(113)** was purified by sublimation to give a final yield of 32%. The oxime **(113)** was identified using a signal in the NMR spectrum at δ7.49 (singlet, 1H), representing the C-H of the oxime group. In addition, a signal of variable chemical shift and intensity in the region δ7.2-7.3 is visible, representing the -OH of the oxime group.



(107) **(114)**

Scheme 26

In a similar manner to the synthesis of the oxime **(113)**, the aldehyde **(107)** was treated with hydroxylamine hydrochloride in a basic solution of ethanol and water (Scheme 26). The aqueous reaction mixture was washed with ether and the oxime **(114)** was precipitated by acidification of the solution. The precipitate was extracted into ether. The oxime **(114)** was purified by sublimation in a yield of 67%.

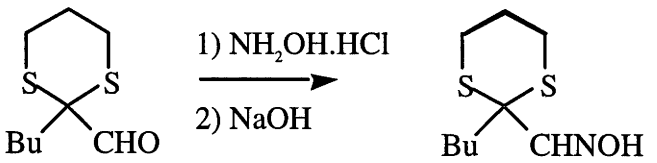
The ^{1}H NMR spectrum of the oxime **(114)** shows two stereoisomers, a *cis* and a *trans* isomer, which were sublimed coincidently. The ^{1}H NMR spectrum of the mixed isomers in d_6-benzene includes two sets of paired doublets at δ7.59 and δ4.29 (major isomer), and at δ6.97 and δ5.49 (minor isomer). The relative integrations indicate a ratio of these isomers of 2:1. Molecular analysis of the product mixture shows that these compounds have identical compositions. A ^{1}H NMR study of various alkyl-oximes by

Karabatsos and Taller[123] shows that the oxime C-H signals of *trans*-oximes are consistently further downfield than oxime C-H signals of *cis*-oximes by 0.7 - 1.0 ppm in d_6-benzene. α-Methine proton signals of *trans*-oximes show a difference in chemical shift of 0.8 - 1.0 ppm upfield compared to that of the α-methine proton signals of *cis*-oximes in d_6-benzene. On this basis, the major isomer was assigned as the *trans*-oxime, while the minor isomer was assigned as the *cis*-oxime.

The reason for the appearance of two isomers in the synthesis of 1,3-dithiane-2-carboxaldehyde oxime **(114)** as opposed to the single isomer observed in the synthesis of 2-methyl-1,3-dithiane-2-carboxaldehyde oxime **(113)** is likely to be a result of steric hindrance in the latter case. Steric interaction between the oxime –OH group and the 2-methyl group in the oxime **(113)** may result in a complete disfavouring of the *cis*-isomer (Figure 5).

cis-**(113)** *trans*-**(113)**

Figure 5: Steric interactions in the formation of oxime (113).



(111) **(115)**

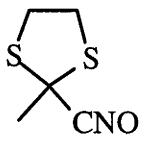
Scheme 27

2-Butyl-1,3-dithiane-2-carboxaldehyde **(111)** was treated with hydroxylamine hydrochloride in basic ethanol/water in order to form the oxime **(115)** (Scheme 27). It was found that washing the aqueous reaction mixture with ether, as described above in the syntheses of the oximes **(113)** and **(114)**, resulted in extraction of the oxime **(115)** into the

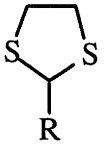
organic phase. Clearly, the oxime (**115**) is less soluble in basic solution than the oximes (**113**) and (**114**). This could suggest that the oxime (**115**) is less acidic than either 2-methyl-1,3-dithiane-2-carboxaldehyde oxime (**113**) or 1,3-dithiane-2-carboxaldehyde oxime (**114**). Alternatively, the increased hydrophobic nature of the oxime (**115**) over the oximes (**113**) and (**114**) as a result of the 2-butyl moiety may result in preferential extraction into the organic solvent. Consequently, the oxime (**115**) was precipitated from the aqueous solution using hydrochloric acid without washing the aqueous layer with ether previously. This is in contrast to the procedure used to synthesise the oxime (**113**), where the aqueous layer is washed with ether in order to remove neutral impurities from the reaction mixture. The oxime (**115**) was purified by column chromatography, to give a yield of 36%. The ^{1}H NMR spectrum of the crude product mixture indicates a large proportion of unreacted starting material, accounting for the low yield. It appears likely that poor solubility of the aldehyde (**112**) in the basic ethanol/water reaction medium, due to the hydrophobic nature of the 2-butyl moiety, is a factor in the poor extent of reaction.

The oxime (**115**) was identified using a characteristic resonance in the ^{1}H NMR spectrum at δ7.41, representing the oxime C-H. A broad signal of variable chemical shift and intensity between δ7.2 and 7.3 represents the oxime -OH. However, this signal was not always visible due to proton exchange. Only one isomer was observed.

4.2 2-Methyl-1,3-dithiolane-2-carboxaldehyde Oxime



(81)

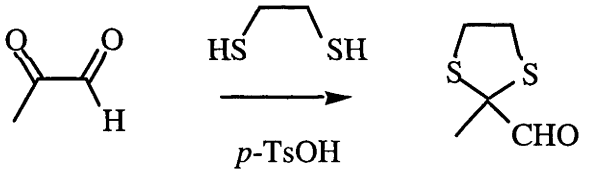


(116)

2-Methyl-1,3-dithiolane-2-carbonitrile *N*-oxide (**81**) was chosen as a slightly smaller analogue of the dithianenitrile oxide (**104**), in order to compare the rates of

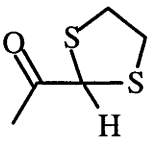
dimerisation between the two nitrile oxides. According to the literature,[90] treatment of 2-substituted-1,3-dithiolanes (**116**) with butyllithium results in facile elimination to give ethylene and dithiocarbonates. For this reason, it was necessary to investigate the synthesis of the dithiolane carboxaldehyde (**83**) *via* a route other than that used for the dithiane series described above.

The dithiolane carboxaldehyde (**83**) was synthesised using the procedure of Fridinger and Henery-Logan.[103] Pyruvaldehyde (**82**) is stored as a 40% aqueous solution. This and 1,2-ethanedithiol were treated with *p*-toluenesulfonic acid in benzene at reflux. The water of both the initial solution and the product of the reaction were removed by means of a Dean-Stark apparatus (Scheme 28). The product formed was exclusively the 2,2-dithioketal (**83**), with no evidence of the 1,1-dithioacetal (**117**) being formed. The preference for the thioketal (**83**) is a result of the thermodynamic stability of the thioketal (**83**) over the thioacetal (**117**).[103]



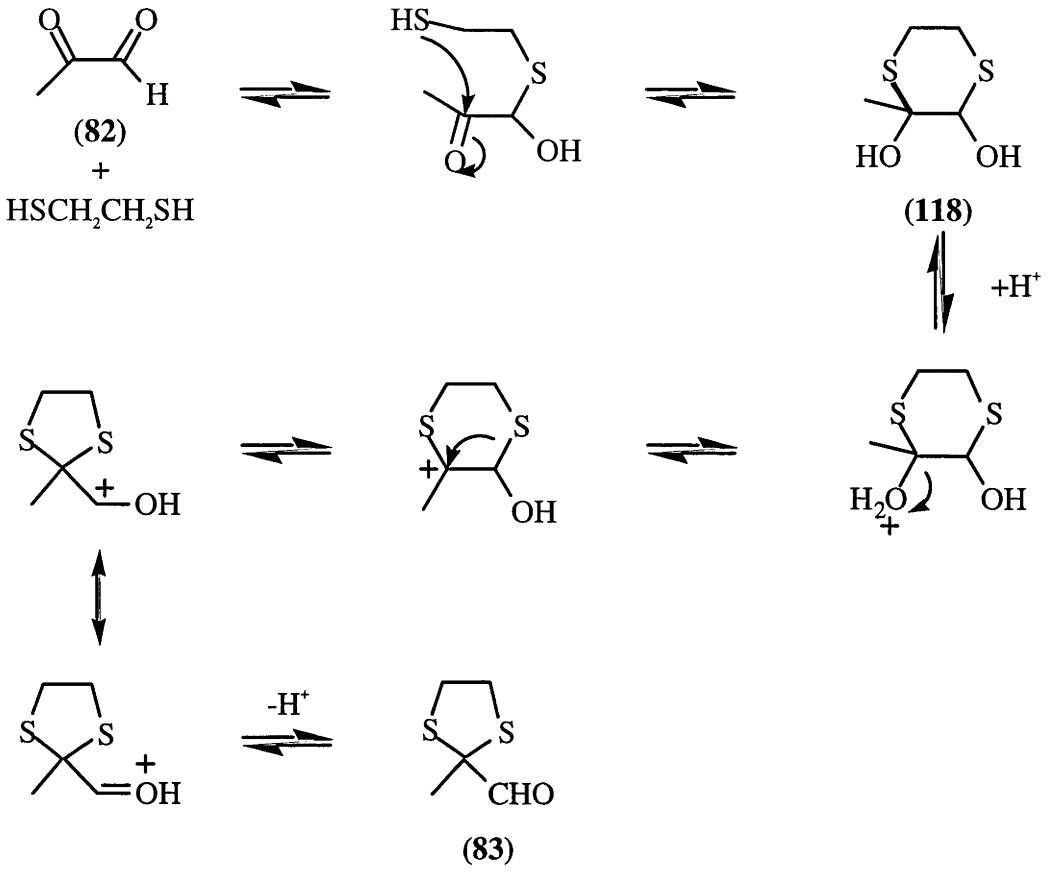
(**82**) (**83**)

Scheme 28



(**117**)

The proposed mechanism for the formation of the aldehyde (**83**) is illustrated in Scheme 29.[103] Following nucleophilic attack of a sulfur of 1,3-propanedithiol on the aldehyde (C1) carbonyl group, a second attack occurs on the ketone (C2) carbonyl group. This affords the intermediate glycol (**118**), which can be protonated and lose water to afford a sulfur-stabilised carbocation. This carbocation undergoes a ring contraction to



Scheme 29

result in a more favourable oxygen-stabilised carbocation, which deprotonates to give the thioketal **(83)**.

2-Methyl-1,3-dithiolane-carboxaldehyde **(83)** was identified using characteristic signals in the ^{1}H NMR spectrum (300 MHz). The aldehyde proton resonance is visible at δ9.11 (singlet, 1H). A signal at δ1.77 represents the methyl protons (singlet, 3H). The remaining protons give rise to a complex multiplet at δ3.3-3.5 (4H), in contrast to the literature[103] which describes a singlet at δ3.42 (60 MHz). The complexity of this signal at 300 MHz is due to the subtle difference in chemical environment between protons on the α- and β-faces in the 4- and 5-positions. The carbonyl group provides shielding for the protons on the α-face (Figure 6). The protons on the α-face therefore show geminal (^2J) and vicinal (^3J) coupling to the protons on the β-face and *vice versa*. This results in a splitting pattern corresponding to two overlapping sets of doublets of doublets, accounting

for the multiplet observed. The aldehyde **(83)** was generally used without further purification, although purification by either distillation or column chromatography was possible. Distillation appears to result in a small level of decomposition.

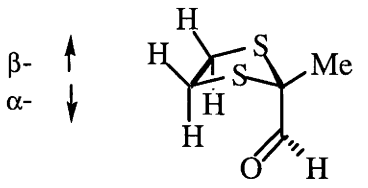
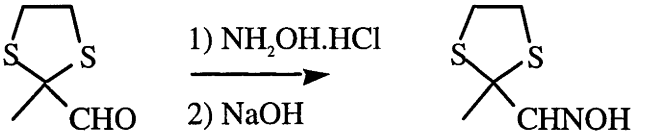


Figure 6: Non-equivalence of protons on the α- and β-faces of 2-methyl-1,3-dithiolane-2-carboxaldehyde.

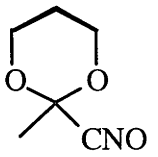


(83) **(84)**

Scheme 30

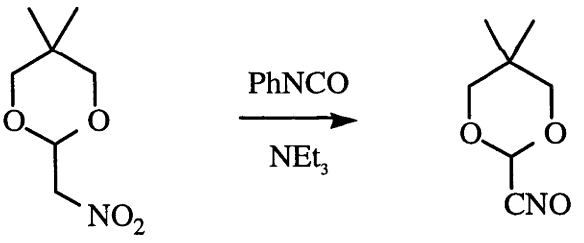
The crude dithiolane aldehyde **(83)** was treated with hydroxylamine hydrochloride in a basic ethanol/water solution (Scheme 30), with a workup procedure as described above for the oximes **(113)** and **(114)**, to give a yellow powder. This powder was purified by either chromatography or sublimation to give colourless crystals of the 2-methyl-1,3-dithiolane-2-carboxaldehyde oxime **(84)** in 50% yield. The product **(84)** was identified using characteristic resonances in the ^{1}H NMR spectrum. The oxime C-H proton is represented by a signal at δ7.54 (singlet, 1H), and the oxime O-H proton is represented by a singlet of variable chemical shift between δ7.2 and δ7.3 (1H). The C-4 and C-5 protons give rise to a complex multiplet at δ3.3-3.5 (4H) which is similar to that of the parent aldehyde **(83)**. Only one isomer was observed.

4.3 Precursors to 2-Methyl-1,3-dioxane-2-carbonitrile N-*Oxides*



(85)

A number of methods were examined for the synthesis of precursors to a 2-methyl-1,3-dioxane-2-carbonitrile *N*-oxide of the type **(85)**. Synthesis *via* carbanion chemistry in direct analogy to the synthesis of precursors to the dithianenitrile oxide **(104)** was not viable, due to the low acidity of the C2-proton in 1,3-dioxane. Jäger *et al.*[124, 125] have synthesised the dioxanenitrile oxide **(120)**, similar to the desired nitrile oxide **(85)**, from 5,5-dimethyl-2-(nitromethyl)-1,3-dioxane **(119)** using the Mukaiyama procedure (Scheme 31). It was therefore envisaged that the nitrile oxide **(85)** could be synthesised *via* the Mukaiyama procedure from 2-methyl-2-nitromethyl-1,3-dioxane **(122)**.

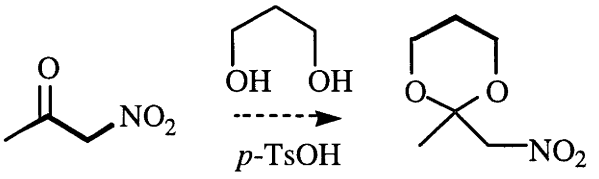


(119) **(120)**

Scheme 31

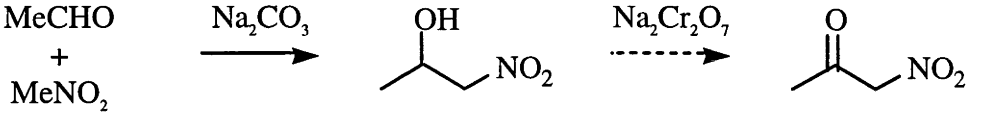
The proposed synthesis of the nitromethyldioxane **(122)** involved acetalisation of nitroacetone **(121)** (Scheme 32). The synthesis of nitroacetone **(121)** was attempted *via* the oxidation of 1-nitro-2-propanol **(123)** according to the procedure of Hurd and Nilson.[126] 1-Nitro-2-propanol **(123)** was synthesised in fair yield by treatment of acetaldehyde with nitromethane under basic conditions. The ^{1}H NMR spectrum of 1-nitro-2-propanol shows an -OH signal of variable chemical shift and intensity at δ2.5 - δ3 (broad singlet) and an irregular multiplet at δ4.3 - δ4.6 (3H). This multiplet consists of two overlapping signals, a

pair of strongly coupled doublets of doublets, from the non-equivalent C1-protons, and a broad multiplet representing the C2-proton.



(121) **(122)**

Scheme 32

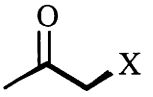


(123) **(121)**

Scheme 33

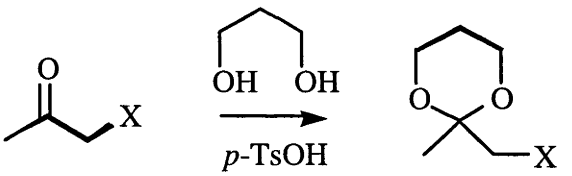
1-Nitro-2-propanol (**123**) was then treated with sodium dichromate (Scheme 33). However, contrary to the literature report,[126] nitroacetone (**121**) was not observed to precipitate out of the aqueous solution. Extracting the reaction mixture with ether yielded an approximately 40:60 mixture of 1-nitro-2-propanol (**123**) and what was presumed to be nitroacetone (**121**), measured by analysis of the relative intensity of ^{1}H NMR signals. Filtering these extracts through silica did not provide separation of nitroacetone (**121**) from 1-nitro-2-propanol (**123**). The ^{1}H NMR spectrum shows two separate signals believed to represent nitroacetone (**121**), one at δ2.35 (3H, s) representing the methyl protons and one at δ5.28 (2H, s) for the methylene protons. It should be noted that these ^{1}H NMR data are inconsistent with those presented in the literature,[127] which gives the chemical shift of the C3-protons at δ1.99. The ^{1}H NMR signals described here were reproducible within the experiments carried out, and are consistent with the structure of nitroacetone. Repeating the procedure for a longer time or with 1.5 equivalents of oxidising agent gave no change in proportion of products. Increasing the concentration of the reaction mixture allowed

only precipitation of what were probably chromate salts. These crystals were dark green in colour and insoluble in neither ether nor methanol.



(124a) X = Cl
(124b) X = I

Attempts to synthesise nitroacetone **(121)** by treatment of haloacetones **(124)** with silver nitrite were also unsuccessful.[127] Treatment of chloroacetone **(124a)** with silver nitrite gave no reaction. When iodoacetone **(124b)** was treated with silver nitrite, a change in colour was observed, indicating the formation of iodine. The ^{1}H NMR spectrum of the crude product mixture showed a range of compounds. This may be because nitroacetone **(121)** is unstable,[126] and it decomposed before purification could be attempted. Due to the difficulties in separating nitroacetone **(121)** and its instability, an alternative route to 2-methyl-2-nitromethyl-1,3-dioxane **(122)** was investigated.



(124a) X = Cl
(124b) X = I

(125a) X = Cl
(125b) X = I

Scheme 34

The synthesis of 2-methyl-1-nitromethyl-1,3-dioxane **(122)** *via* halomethyl acetals **(125)** was attempted (Scheme 34). Iodoacetone **(124b)** was synthesised from chloroacetone **(124a)** using sodium iodide in acetone. Iodoacetone **(124b)** was formed in good yield, however the purple-brown colour of the solution indicated the presence of iodine. Washing of the iodoacetone **(124b)** solution with an aqueous solution of sodium bisulfite to remove the iodine resulted in decomposition of iodoacetone **(124b)**. The ^{1}H NMR spectrum of iodoacetone **(124b)** shows two singlets at δ2.4 (3H) representing the methyl

group, and δ3.8 (2H) representing the methylene group. The spectrum is similar to that of chloroacetone (**124a**) (methyl resonances at δ2.4 (3H, s)) and methylene resonances at δ4.1 (2H, s)). The change in chemical shift of the methylene proton signal is a characteristic result of the change in chemical environment as the chlorine is replaced by iodine.

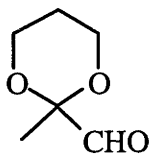
Both chloroacetone (**124a**) and iodoacetone (**124b**) were treated with 1,3-propanediol in the presence of *p*-toluenesulfonic acid at reflux in benzene (Scheme 34). Water was removed by means of a Dean-Stark apparatus. In the case of chloroacetone (**124a**), the formation of 2-chloromethyl-2-methyl-1,3-dioxane (**125a**) proceeds readily and cleanly. The ^{1}H NMR spectrum clearly shows a dioxane system; two overlapping multiplets at δ1.6 - 1.9 (2H) represent the C5 axial and equatorial protons, while two overlapping multiplets at δ3.8 - 4.0 (4H) represent the protons in the C4,6 equatorial and C4,6 axial positions. Also present are singlets at δ3.62 (2H, s) and δ1.51 (3H, s) representing the chloromethyl and methyl protons respectively. The acetal (**125a**) proved unstable and decomposed in storage at 4°C, and was therefore used without further purification.

Iodoacetone (**124b**) appeared to react to give a number of compounds. Due to the instability of the byproducts, it was not possible to isolate any compound for analysis. Signals in the crude ^{1}H NMR spectrum at δ1.55 (3H, singlet) and δ3.4 (2H, singlet) suggest the formation of the desired iodomethyl-acetal (**125b**), however multiple overlapping signals in the regions δ1.6-1.9 and δ3.8-4.0 preclude complete identification.

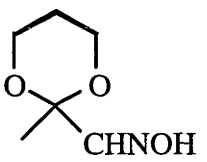
In order to synthesise the desired nitromethyl-dioxane (**122**), 2-chloromethyl-2-methyl-1,3-dioxane (**125a**) was treated with silver nitrite.[127] Sodium iodide was added in catalytic amounts in order to generate the iodomethyl acetal (**125b**) *in situ*, as the chloromethyl-dioxane (**125a**) was not expected to be sufficiently active towards nucleophilic substitution. However, after several days at room temperature, no reaction was observed. 2-Chloromethyl-2-methyl-1,3-dioxane (**125a**) was treated with sodium iodide in acetone in order to synthesise the 2-iodomethyl derivative (**125b**) directly.

However, the 2-iodomethyl compound (**125b**) was not formed, despite a long reaction time. Traces of iodoacetone (**124b**) were visible by ^{1}H NMR spectroscopy in the crude product mixture, signifying hydrolysis of the acetal (**125a**) followed by substitution of the formed chloroacetone (**124a**).

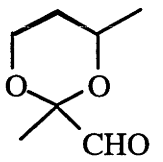
The lack of reactivity was considered to be the result of the methyldioxane moiety, a *pseudo*-neopentyl system, preventing approach to the reactive site by a prospective nucleophile. It was considered that this steric hindrance would also hamper reactivity of the 2-nitrocompound (**122**) towards a base, particularly a hindered base such as triethylamine. This suggests that 2-methyl-2-nitromethyl-1,3-dioxane (**122**) is unlikely to be a suitable substrate for the Mukaiyama reaction.



(126)



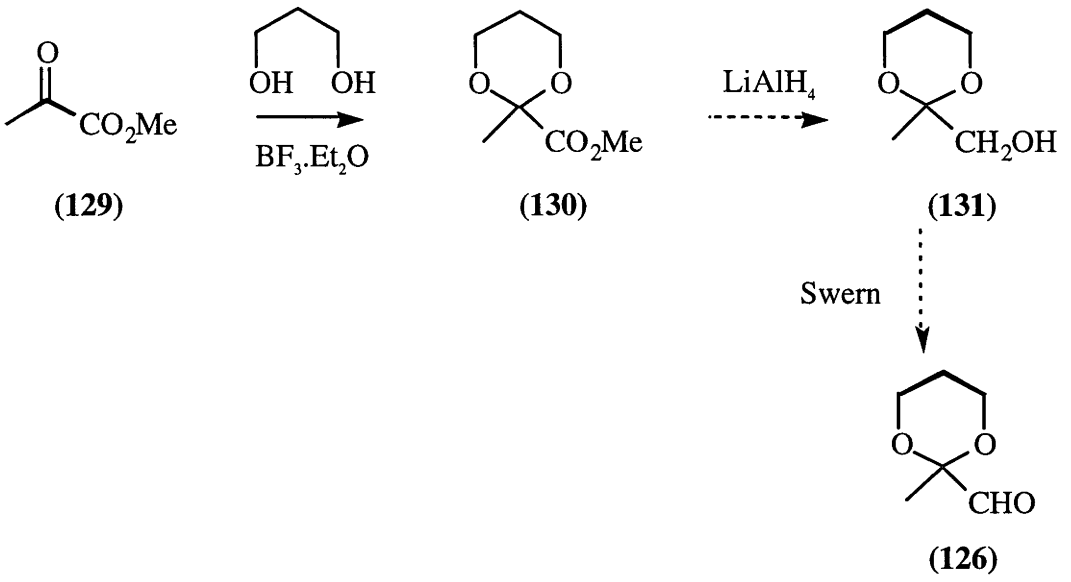
(127)



(128)

The synthesis of the aldehyde (**126**) was therefore attempted, as a precursor to formation of the oxime (**127**). Initially, this was carried out using a modification of a literature procedure for the synthesis of 2,4-dimethyl-1,3-dioxane-2-carboxaldehyde (**128**) (Scheme 35).[128] A large excess of methyl pyruvate (**129**) (10 eq) in dichloromethane was treated with 1,3-propanediol in the presence of boron trifluoride etherate. The crude reaction product was treated with sodium borohydride in methanol in order to reduce the residual methyl pyruvate. ^{1}H NMR spectroscopy of the crude reaction product showed what was presumed to be the acetal (**130**) (δ3.9-4.1, multiplet, δ1.51, singlet) and a number of other products. Chromatography was unsuccessful in separating the mixture into its components, and a low mass balance suggested that the product was decomposing.

The acetalisation procedure was repeated and the initial crude reaction product was distilled to remove methyl pyruvate (**129**). Column chromatography was attempted on the residue of the distillation, which contained the desired acetal (**130**) as shown by NMR



(129) **(130)** **(131)** **(126)**

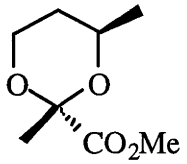
Scheme 35

spectroscopy. This was unsuccessful, resulting in a partially purified sample of the acetal **(130)** with a mass balance of less than 10%. The acetal was identified by ^{1}H NMR spectroscopy. Signals representing methyl 2-methyl-1,3-dioxane-2-carboxylate **(130)** were visible at δ3.8-3.9 (m, 5H, C4,6-H_a, -CO_2CH_3) and δ3.9-4.1 (m, 2H, C4,6-H_e). The multiplet at δ3.8-3.9 includes a singlet due to the protons of the methyl ester at δ3.85, raising the relative integration from 2H to 5H.

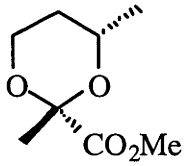
(132) **(133)**

Due to the low yield of synthesis and the poor stability of the desired dioxane ester **(130)**, the procedure was repeated using 1,3-butanediol **(132)** and 2,2-dimethyl-1,3-propanediol **(133)** as the 1,3-diols for the acetalisation procedure. The added steric bulk of these reagents in the form of methyl substituents was expected to give a degree of stability to the intermediates in the synthesis. The reaction of 1,3-butanediol **(132)** with methyl pyruvate **(129)** resulted in a low yield of acetal **(134a)**, which was identified by the

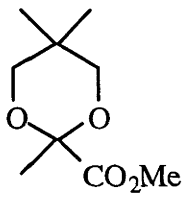
^{1}H NMR spectrum of the crude reaction product through comparison of the signals with literature values.[128] Signals at δ1.24 (doublet, 3H, C4-H), 1.51 (singlet, 3H, C2-CH_3), and δ3.83 (singlet, 3H, -CO_2CH_3) indicate the formation of methyl (2*RS*,4*RS*)-2,4-dimethyl-1,3-dioxane-2-carboxylate (**134a**). The alternative diastereomer, methyl (2*SR*,4*RS*)-2,4-dimethyl-1,3-dioxane-2-carboxylate (**134b**), is not formed.[128] The acetal (**134a**) could not be purified; column chromatography failed to remove the large amount of impurities in the sample, while distillation caused decomposition of the product.



(134a)

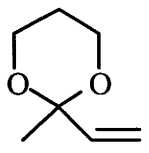


(134b)



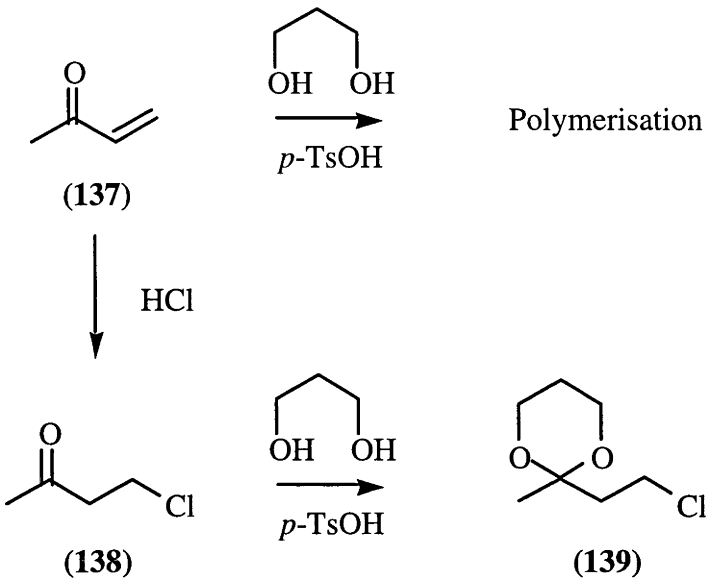
(135)

Using 2,2-dimethyl-1,3-propanediol (**133**) as the diol in the acetalisation reaction resulted in a low-yield (19%) of 2,5,5-trimethyl-2-methoxycarbonyl-1,3-dioxane (**135**), which was purified using column chromatography. The reduction reactions of the dioxanes (**135**) and (**134a**) with lithium aluminium hydride were not carried out, due to the poor yields of the synthesis.



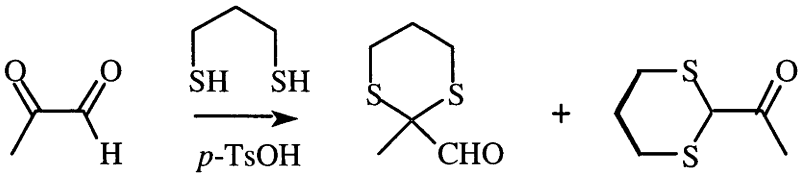
(136)

The vinyl acetal (**136**) was considered as a masked form of the carboxaldehyde-acetal (**126**), and to this end its synthesis was investigated. It was envisaged that the



Scheme 36

aldehyde functionality would be accessible *via* ozonolysis of the vinyl group of 2-methyl-2-vinyl-1,3-dioxane **(136)**. An attempt to produce the 2-vinyldioxane **(136)** *via* acetalisation of methylvinylketone **(137)** using standard Dean-Stark procedures resulted only in polymerisation of the starting material (Scheme 36). The alkene functionality was masked as the hydrogen chloride adduct; treatment of methylvinyl ketone with a stoichiometric amount of hydrochloric acid gives 1-chloro-2-butanone **(138)** (Scheme 36). This was treated with 1,3-propanediol in the presence of *p*-toluenesulfonic acid with a Dean-Stark apparatus to give what was presumed to be the acetal **(139)**, by analysis of the ^{1}H NMR spectrum of the crude product mixture. The NMR spectrum shows signals at δ1.42 (singlet, 3H), tentatively assigned as the C2-methyl group, and δ2.18 (multiplet, 2H), assigned as the C5-methylene group. Partially obscured signals at δ3.7 (multiplet, approx. 2H) and δ3.8 - 4.0 (multiplet, approx. 4H) were assigned respectively as the equatorial C4,6-protons and a combination of the α-chloro methylene group and the axial C4,6-protons. Definitive assignment of signals was not possible, however, and an attempt to purify the acetal **(139)** by distillation resulted in decomposition. As a result of this decomposition, this route to the desired acetalaldehyde **(126)** was not investigated further.



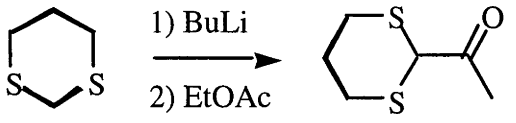
(82) **(108)** **(140)**

Scheme 37

The synthesis of the acetal (**126**) was investigated using a different protecting group. The synthesis of 2-(2-methyl-1,3-dioxan-2-yl)-1,3-dithiane (**141**) was investigated. It was envisaged that the 1,3-dithiane moiety could be removed without removal of the 1,3-dioxane moiety by oxidative hydrolysis under non-acidic conditions,[92, 94-98] to give the dioxane-2-carboxaldehyde (**126**). Treatment of pyruvaldehyde (**82**) with 1,3-propanedithiol under acidic conditions resulted in a mixture of 2-acetyl-1,3-dithiane (**140**), 2-methyl-1,3-dithiane-2-carboxaldehyde (**108**) and a large proportion of impurities. The ^{1}H NMR spectrum of the crude reaction product showed that the dithiane-2-carboxaldehyde (**108**) was the major product (Scheme 37); clearly visible were resonances representing the formyl dithiane (**108**) at δ1.50 (singlet, 3H) and δ9.05 (singlet, 1H). The only signal clearly visible representing 2-acetyl-1,3-dithiane (**140**) is a singlet at δ2.38. The result here is similar to that described in section 4.2 for the synthesis of 2-methyl-1,3-dithiolane carboxaldehyde (**83**). The thermodynamically more favourable 2,2-dithioketal (**108**) is formed in preference to the expected product, the 1,1-dithioacetal (**140**).

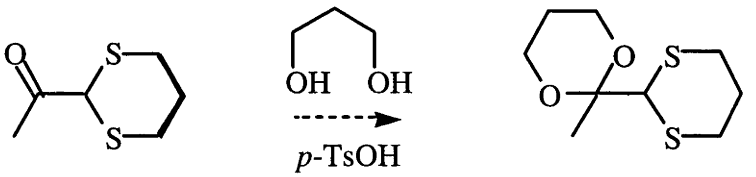
The synthesis of 2-acetyl-1,3-dithiane (**140**) was effected by the treatment of 1,3-dithiane (**77**) with butyllithium, followed by ethyl acetate (Scheme 38), in 8% yield. The low yield appeared to be the result of poor formation of the 1,3-dithiane anion. Residual 1,3-dithiane (**77**) was removed by sublimation. The product was identified using ^{1}H NMR spectroscopy; the ^{1}H NMR spectrum of 2-acetyl-1,3-dithiane (**140**) shows a singlet at δ4.28 (1H), representing the C2-proton, and a singlet at δ2.36 (3H) representing the acetyl group

protons. Due to the poor result of the subsequent reaction, the yield of compound **(140)** was not improved upon.



(77) **(140)**

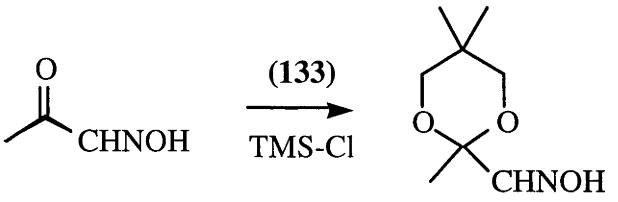
Scheme 38



(140) **(141)**

Scheme 39

The thioacetal **(140)** was treated with 1,3-propanediol and *p*-toluenesulfonic acid using a Dean-Stark apparatus in an attempt to generate 2-(2-methyl-1,3-dioxan-2-yl)-1,3-dithiane **(141)** (Scheme 39). The ^{1}H NMR spectrum of the crude product mixture shows a complex mixture of starting materials and products. Due to the large number of overlapping signals, absolute identification is difficult. A singlet at δ4.62 indicates formation of what could represent the C2-proton of a distinct thioacetal (c/f. 2-acetyl-1,3-dithiane **(140)** at δ4.28). However, even after several hours at reflux a large proportion of starting materials is present. The reaction mixture became discoloured after this time, and thin layer chromatography of the reaction mixture showed a large number of products. The slow reaction may be the result of the large amount of steric strain between the two vicinal acetals. Due to the poor formation of the dioxane-dithiane **(141)** using this method, no further attempt was made to synthesise the desired acetal-aldehyde **(126)** *via* this route.



(142) **(143)**

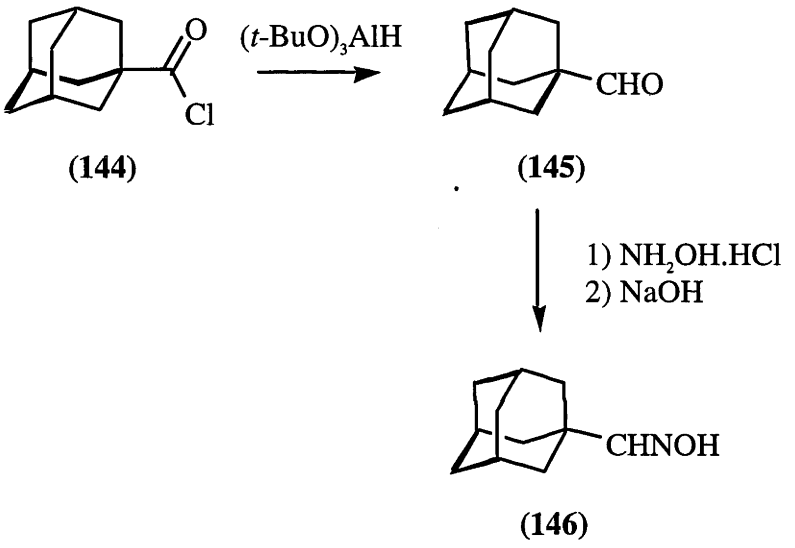
Scheme 40

The synthesis of a suitable variation of the oxime **(127)**, (hydroxyimino)(2,5,5-trimethyl(1,3-dioxan-2-yl))methane **(143)**, was achieved using the procedure of Martin *et al.*,[129] derived from that of Chan *et al.*.[130] The oxime **(143)** was synthesised directly from commercially available 1-pyruvaldehyde *anti*-oxime **(142)** by treatment with 2,2-dimethyl-1,3-propanediol **(133)** and trimethylsilyl chloride in dichloromethane at reflux for two days (Scheme 40). However, this oxime **(143)** appeared to be unstable on heating, so it could not be purified by sublimation. Attempts at sublimation gave a mixture of sublimate and decomposition product. The ^{1}H NMR spectrum of the decomposition product shows four singlets, at δ0.93, δ2.12, δ3.36 and δ3.95, with relative integration 2:1:1:1. Purification of the oxime **(143)** by column chromatography gave a yield of 33.5%, however traces of impurities are difficult to remove, due to the decomposition of the product. The oxime **(143)** was generally used without further purification. The ^{1}H NMR spectrum of the oxime **(143)** shows a characteristic oxime resonance at δ7.40 and a resonance of variable chemical shift between δ7.6 and δ7.7. Only one isomer is observed.

This procedure was repeated using 1,3-propanediol instead of 2,2-dimethyl-1,3-propanediol in an attempt to synthesis 2-methyl-1,3-dioxane-2-carboxaldehyde oxime **(127)**. This reaction was unsuccessful. Therefore, the oxime **(143)** was used as a precursor of an analogue of the desired nitrile oxide **(85)**.

4.4 Adamantanecarboxaldehyde oxime

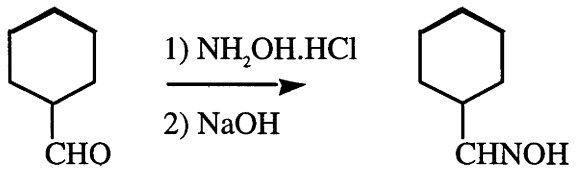
Adamantanecarboxaldehyde oxime (**146**) was synthesised from adamantanecarbonyl chloride (**144**) using the procedure of Dondoni *et. al.*[50] Adamantanecarbonyl chloride (**144**) was reduced to adamantanecarboxaldehyde (**145**) with tri-*tert*-butoxyaluminium hydride.[131] The aldehyde (**145**) was treated immediately with hydroxylamine hydrochloride in basic ethanol/water at reflux, to afford the oxime (**146**) in 26% yield (Scheme 41). Only one isomer was observed, reflecting the strong steric requirements of the system.



(144) **(145)** **(146)**

Scheme 41

4.5 Cyclohexanecarboxaldehyde oxime



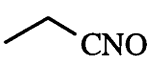
(147) **(148)**

Scheme 42

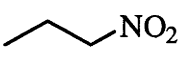
Cyclohexanecarboxaldehyde oxime (**148**) was synthesised from commercially available cyclohexane carboxaldehyde (**147**) by treatment with hydroxylamine

hydrochloride in a basic ethanol/water solution (Scheme 42). However, as in the synthesis of 2-butyl-1,3-dithiane-2-carboxaldehyde oxime (**115**) described in section 4.1, the oxime is readily extracted into ether from the basic reaction mixture, therefore the reaction mixture was not washed with ether prior to precipitation of the oxime (**148**). The oxime (**148**) was readily purified by distillation in a yield of 57%. The ^{1}H NMR spectrum of oxime (**148**) in d_6-benzene shows two isomers in the ratio 2:1, which are likely to be the *cis* and *trans* isomers about the oxime double bond. The oxime C-H signal of the *trans*-isomer of the oxime (**148**) is visible at δ7.40 (doublet, 1H), while the C1-proton shows a signal at δ2.0 - 2.2 (multiplet, 1H). The *cis*- isomer of the oxime (**148**) shows an oxime C-H signal at δ6.44 (doublet, 1H) and a C1-H signal at δ3.1 - 3.2 (multiplet, 1H). A broad singlet at δ7.9 represents the combined -OH signals. The structures of the isomers were assigned on the basis of their ^{1}H NMR data according to the ^{1}H NMR study of Karabatsos and Taller[123] as described in section 4.1. The oxime C-H signal of the *trans*-isomer of the oxime (**148**) shows a downfield change in chemical shift of 0.98 ppm, compared to the oxime C-H signal of the *cis*-isomer. The α-methine signal of the *trans*-isomer shows an upfield shift of 1.2 ppm compared to the α-methine signal of the *cis*-isomer. The similarity of isomer ratio between the oxime (**148**) and 1,3-dithiane-2-carboxaldehyde oxime (**108**) represents the similarity of the steric requirements on oxime formation.

4.6 Hydroximinopropane

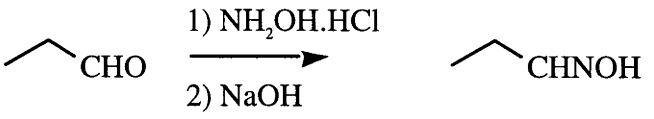


(17)



(102)

While nitrile oxide (**17**) can be synthesised directly from 1-nitropropane (**102**) using the Mukaiyama method (see Chapter 3), it was considered desirable to be able to generate the nitrile oxide (**17**) *via* a similar method to that used to generate the dithianenitrile oxides (**104**) and (**106**), the dioxanenitrile oxide (**160**) and

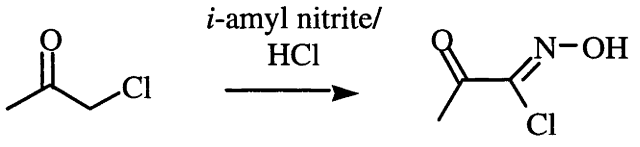


(149) **(150)**

Scheme 43

2-oxopropanenitrile *N*-oxide (**61**). To this end, hydroximinopropane (**150**) was synthesised from propanal (**149**) by treatment of the aldehyde with hydroxylamine hydrochloride in a basic ethanol/water solution, with a yield of 62% (Scheme 43). The ^{1}H NMR spectrum of the oxime (**150**) in d_6-benzene shows the product as 2 stereoisomers, with a *cis-trans* ratio of 1:1.1. The *trans*-isomer shows a characteristic C-H oxime resonance at δ7.33 (1H, t). The *cis*-isomer shows a characteristic C-H oxime resonance at δ6.47 (1H, t). The mixture of isomers in d_6-benzene gives a ^{1}H NMR spectrum consistent with data presented in the literature.[123]

4.7 Precursor to 2-Oxopropanenitrile N-*Oxide*



(124a) **(151)**

Scheme 44

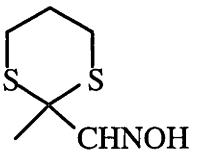
1-Chloro-1-(hydroxyimino)acetone (**151**) was synthesised directly from chloroacetone (**124a**) using *iso*-amyl nitrite in the presence of hydrochloric acid in ether (Scheme 44).[104] This method allowed direct introduction of the hydroximinoyl chloride moiety desired for nitrile oxide generation, therefore chlorination of 1-pyruvaldehyde *anti*-oxime (**142**) was not necessary. The nitronation is selective for the 1-position, resulting in the exclusive formation of 1-chloro-1-(hydroxyimino)acetone (**151**) in a 36% yield. The hydroximinoyl chloride (**151**) was purified by recrystallisation from carbon

tetrachloride. The ^{1}H NMR spectrum of the hydroximinoyl chloride (**151**) contains a signal at δ2.51 (singlet, 3H) which is in the expected range of chemical shifts for a proton in the α-position to a conjugated carbonyl group. Also present is a signal of variable chemical shift in the range δ8.4 - δ8.6, indicative of a hydroximinoyl chloride -OH group.

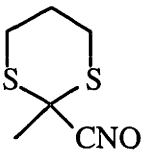
Chapter 5: Results and Discussion - Generation and Properties of Nitrile Oxides

The dithiane-, dithiolane-, dioxane-, acyl- and alkyl-nitrile oxides described in the introduction were generated mostly from the oximes whose synthesis was described in the previous chapter. The stability of these nitrile oxides was then investigated using spectroscopic methods.

5.1 1,3-Dithiane-2-carbonitrile N-*Oxides*



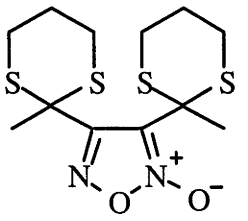
(113)



(104)

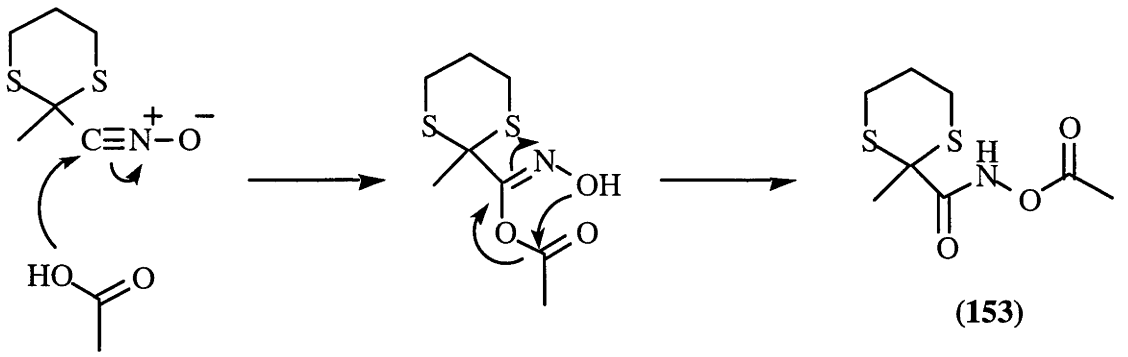
Commonly, nitrile oxides are synthesised from the corresponding oximes *via* the corresponding hydroximinoyl chlorides. However, treatment of 2-methyl-1,3-dithiane-2-carboxaldehyde oxime **(113)** with *N*-chlorosuccinimide resulted in its decomposition, presumably *via S*-chlorination. For this reason, the synthesis of the nitrile oxide **(104)** from the oxime **(113)** was attempted, using a relatively mild oxidation procedure. The oxime **(113)** was treated with mercuric(II) acetate in ethanol at reflux according to the procedure of Lokanatha Rai *et al.*[132] The dipolarophile ethyl cinnamate **(70)** was added to the reaction mixture so that the formation of the nitrile oxide **(104)** could be observed by the trapping of this species as an isoxazoline. The ^{1}H NMR spectrum of the crude product mixture showed no evidence of cycloaddition products. The use of an excess of dipolarophile and oxidising agent did not result in adduct formation. The procedure was repeated under the same conditions using 2,6-dichlorobenzaldoxime **(91)** as the nitrile oxide precursor. However, no reaction was observed.

Due to the lack of nitrile oxide generation using mercuric acetate as an oxidising agent, the use of lead(IV) tetraacetate[34] was investigated. The oxime (**113**) was treated with lead(IV) tetraacetate. The presence of the nitrile oxide was confirmed by IR spectroscopy, where a characteristic nitrile oxide signal is visible at 2279 cm^{-1}.



(152)

The nitrile oxide (**104**) was found to decompose rapidly upon generation. The nitrile oxide (**104**) was generated in *d*-chloroform and the reaction mixture was filtered into an NMR tube. ^{1}H NMR spectra of this reaction mixture were recorded at 10 minute intervals for one hour. Observation of the ^{1}H NMR spectrum over this period showed the rapid decomposition of the nitrile oxide (**104**), such that the concentrations of nitrile oxide (**104**) and the decomposition product were approximately equal after one hour. The nitrile oxide (**104**) was no longer visible after 6 hours. Analysis of the spectra indicated that the major reaction product was not the expected furoxan (**152**). The decomposition product was isolated and analysed by ^{1}H NMR and mass spectroscopy. Only one set of methyldithiane resonances was observed, rather than the two sets of overlapping resonances that are expected from the furoxan (**152**). Unexpected signals at δ2.27 (3H, s) and δ10.0 (1H, br s) in the ^{1}H NMR spectrum of this product were not consistent with dimer formation. The molecular ion in the mass spectrum of the decomposition product at *m/z* 235 suggests the structure (**153**), below, which is also consistent with the ^{1}H NMR data. This product is believed to result from the nucleophilic attack of acetic acid on the carbon of the nitrile oxide dipole of the species (**104**), followed by a rearrangement to give the hydroxamic acid derivative (**153**) (Scheme 45).[34, 133]



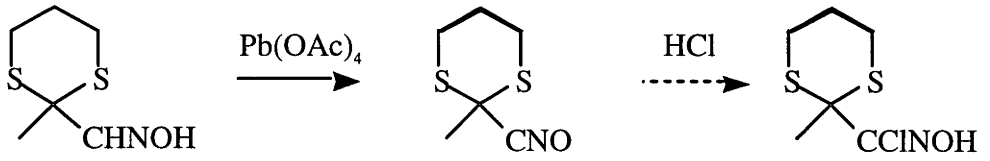
(153)

Scheme 45

Clearly, the stability of the nitrile oxide (**104**) is adversely affected by the presence of acetic acid in the reaction mixture. Just and Dahl[34] used two methods to isolate nitrile oxides after lead tetraacetate generation for purification of stable nitrile oxides, which were tested for effectiveness in isolating the nitrile oxide (**104**). The first involves the addition of triethylamine in order to neutralise the acetic acid formed as a byproduct of lead tetraacetate oxidation. However, the presence of triethylamine did not appear to sufficiently reduce the rate of reaction of the nitrile oxide with acetic acid. The hydroxamic acid derivative (**153**) was still formed rapidly, preventing the isolation of the nitrile oxide (**104**). This is likely to be due to the acetate anion being a better nucleophile that acetic acid; as the triethylamine acetate did not precipitate from the solution, acetate anions remain available for such a process. By washing the reaction mixture with water, the amount of triethylammonium acetate present in the solution could be reduced, however the compound (**153**) was still formed.

The second method involves the washing of the reaction mixture with saturated sodium bicarbonate solution immediately after nitrile oxide generation. The organic phase was separated and then was filtered through a plug of silica. This gave a clean solution of the nitrile oxide (**104**). Integration of the signals in the ^{1}H NMR spectrum compared to those of the internal standard, methyl benzoate, indicated a yield of 37%, giving a concentration of 0.06 M. The low yield may be due to the formation of lead-sulfur complexes and other byproducts in the reaction mixture, which are removed either by

washing or by filtration. Just and Dahl have used lower temperatures in order to reduce the formation of such byproducts from side reactions. However, even when generated at –78°C, the relatively rapid reaction of the nitrile oxide **(104)** to form the hydroxamic **(153)** acid derivative with acetate prevents the isolation of this nitrile oxide.

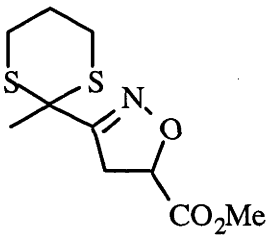


(113) **(104)** **(154)**

Scheme 46

As the formation of the nitrile oxide **(104)** was still somewhat inefficient, an attempt was made to synthesise the hydroximinoyl chloride **(154)** by trapping the intermediate nitrile oxide **(104)** with hydrochloric acid (Scheme 46). While the yield of the nitrile oxide **(104)** generated using lead(IV) tetraacetate would still be expected to be low, the use of the hydroximinoyl chloride **(154)** would allow the quantitative generation of the nitrile oxide **(104)** when required, facilitating the stability studies. The reaction of a nitrile oxide with a hydrogen halide is in essence the reverse of the standard generation method of elimination of a hydroximinoyl halide. The halide anion attacks the δ-positive carbonitrile end of the dipole in a nucleophilic manner.[4, 134] A solution of the oxime **(113)** in *d*-chloroform was treated with lead(IV) tetraacetate followed by concentrated hydrochloric acid. The reaction mixture was filtered after an hour. The ^{1}H NMR spectrum of the crude product mixture shows a complex mixture of products. However, a distinct dithiane pattern is visible in the spectrum, and a signal that may correspond to a 2-methyl group is present at δ1.74. This signal does not correspond to either the oxime starting material **(113)**, or the corresponding aldehyde **(108)**. A singlet is visible at δ9.00, which may correspond to the hydroximinoyl chloride O-H proton. The aldehyde **(108)** also gives a ^{1}H NMR signal at δ9.0, and it is conceivable that this product may form as a result of hydrolysis of the oxime moiety. However, the 2-methyl signal of the aldehyde **(108)** at

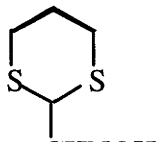
δ1.50 is not visible, ruling out the presence of this compound. Treatment of the crude reaction mixture with methyl acrylate **(34)** did not result in the formation of an isoxazoline as indicated by ^{1}H NMR spectroscopy. When this reaction mixture was treated with triethylamine, however, signals at δ5.10 (dd) and δ3.3 - 3.4 (ABX multiplet) in the ^{1}H NMR spectrum were observed, which correspond to the signals from the C5- and C4-protons of the isoxazoline **(155)**. The formation of this compound indicates that the nitrile oxide **(104)** has been formed on the addition of triethylamine, strongly implying the presence of the hydroximinoyl chloride **(154)**. However, purification of this compound **(154)** was not possible. Attempts at chromatography with both silica and neutral alumina resulted in the formation of the nitrile oxide **(104)**. It is believed that this is a result of elimination of hydrogen chloride from the hydroximinoyl chloride **(154)**, as a result of the partitioning of the extremely polar hydrogen chloride by silica.



(155)

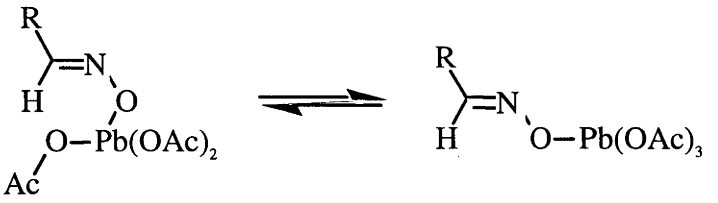
The stability of the nitrile oxide **(104)** was examined by ^{1}H NMR spectroscopy. The nitrile oxide **(104)** was generated from the oxime **(113)** in the presence of an internal standard, methyl benzoate, and a ^{1}H NMR spectrum was recorded immediately. The concentration of the nitrile oxide **(104)** in the ^{1}H NMR sample was then determined by comparison of the signal intensities of the nitrile oxide and the standard. As the dimerisation is a bimolecular process, the rate of this reaction is expected to be concentration dependant. The nitrile oxide **(104)** persists in solution for more than two weeks. As the multiplet at δ2.9 representing the axial protons of the methylene group adjacent to sulfur was the only signal in the ^{1}H NMR spectrum that remained completely unobscured during the procedure, this signal was used for concentration calculations. The

initial concentration of the nitrile oxide (**104**) was 0.06 M. After 8 days at room temperature approximately 50% of the nitrile oxide (**104**) remained in solution. After 14 days, signals representing the nitrile oxide (**104**) were still visible, but the presence of other signals and the poor resolution of the spectrum prevented further analysis. The decomposition product appears to be the expected dimer (**152**), indicated by two singlets at δ1.66 and δ1.68, however the poor resolution of the spectrum precludes absolute identification. Attempts at purifying an authentic sample of the dimer (**152**) were unsuccessful due to its apparent decomposition on silica and neutral alumina.



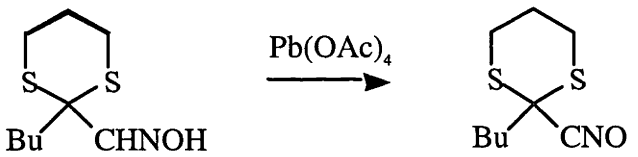
(114)

1,3-Dithiane-2-carboxaldehyde oxime (**114**) was treated with lead(IV) tetraacetate in *d*-chloroform in a similar manner to the treatment of the oxime (**113**) described above. The only ^{1}H NMR signals observed were those of the solvent and the reference compound (tetramethylsilane). No cycloaddition was observed when the oxime (**114**) was treated with lead(IV) tetraacetate in the presence of methyl acrylate (**34**) as a nitrile oxide trap. Just and Dahl[34] postulate an intermediate in which the oxime requires a *trans*-conformation and a six-membered reactive intermediate, represented as conformation (**156a**), in order to form the nitrile oxide from reaction with lead(IV) tetraacetate. A group R of large steric hindrance favours this conformation (**156a**) over the conformation (**156b**). Conformation (**156b**) is likely to decompose by routes other than those which form a nitrile oxide. *cis*-Oximes do not form nitrile oxides using this method. It is likely that the oxime (**114**) is unreactive under these reaction conditions as the lower steric hindrance of this oxime compared to the methyldithiane oxime (**113**) means that the oxime-lead complex formed is less likely to form the reactive conformation (**156a**). A low temperature would be expected to reduce the decomposition of the intermediate (**156b**) sufficiently to allow the formation



(156a) **(156b)**

and subsequent decomposition of an appreciable concentration of the conformation **(156a)** in order to form the nitrile oxide **(105)**. However, even when treated with lead(IV) tetraacetate at –78°C in the presence of methyl acrylate **(34)** as a nitrile oxide trap, the oxime **(114)** failed to show any sign of reaction to form the nitrile oxide **(105)**. This may indicate a different route of decomposition to that described by Just and Dahl,[34] the oxime **(114)** may be forming lead-sulfur complexes with the oxidating agent. As the nitrile oxide **(105)** could not be formed by lead(IV) tetraacetate oxidation, this species was not studied further.



(115) **(106)**

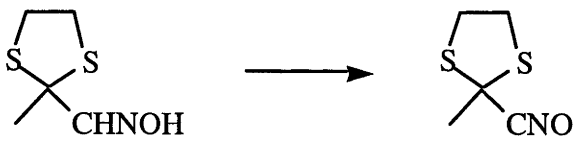
Scheme 47

2-Butyl-1,3-dithiane-2-carbonitrile *N*-oxide **(106)** was generated from the corresponding oxime **(115)** (Scheme 47) using an analogous procedure to that described above for the generation of the nitrile oxide **(104)** from the oxime **(113)**. The oxime **(115)** in *d*-chloroform was treated with lead tetraacetate, then the solution was washed with saturated sodium bicarbonate solution to remove acetic acid. This gave the nitrile oxide **(106)** in a yield of 43%, calculated by comparison of the signal intensities with those of an internal standard (methyl benzoate). The presence of the nitrile oxide **(106)** was confirmed by IR spectroscopy, which showed a characteristic nitrile oxide signal at 2277 cm^{-1}.

The stability of the 2-butyl-1,3-dithiane-2-carbonitrile *N*-oxide (**106**) was examined by ^{1}H NMR. The nitrile oxide (**106**) was generated in the presence of an internal standard, methyl benzoate. The concentration of the nitrile oxide (**106**) in the ^{1}H NMR sample was determined by comparison of the signal intensities of the nitrile oxide and an internal standard, methyl benzoate. The nitrile oxide (**106**) was seen to persist in solution for several weeks at room temperature. The initial concentration of the nitrile oxide was 0.06 M. After 9 days, neither dimerisation nor decomposition was observed. After 6 weeks, more than 50% of the nitrile oxide remained in solution. Due to the complexity of the signals in the ^{1}H NMR spectrum, it is not clear whether the nitrile oxide (**106**) is undergoing dimerisation; a dimer was not isolated.

The butyldithianenitrile oxide (**106**) is considerably more stable than the methyldithianenitrile oxide (**104**). The increase in stability of the nitrile oxide (**106**) over the 2-methyl-1,3-dithiane carbonitrile *N*-oxide (**104**) is accounted for by the increased steric bulk of the 2-butyl moiety, which prevents dimerisation almost completely.

5.2 2-Methyl-1,3-dithiolane-2-carbonitrile N-*Oxide*

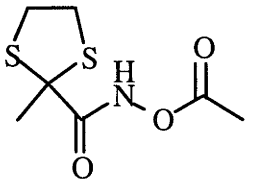


(84) **(81)**

Scheme 48

The dithiolane oxime (**84**) was initially treated with lead(IV) tetraacetate to form the nitrile oxide (**81**) (Scheme 48) in a similar procedure to the initial procedure for the synthesis of the nitrile oxide (**104**) from the oxime (**113**). The ^{1}H NMR spectrum of the filtered reaction mixture was observed over several hours. As with the methyldithianenitrile oxide (**104**), the resultant nitrile oxide (**81**) appeared to react with

acetic acid to form the hydroxamic acid derivative (**157**), as evidenced by the increase in intensity of two specific resonances at δ2.24 (CH_3CO) and δ1.87 (C2-CH_3). However, the presence of a large number of singlets in the region δ1.8 - 2.3 precludes absolute identification of the product, which was not purified.

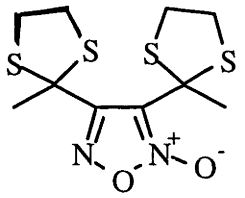


(157)

As with the oxime (**113**), the oxime (**84**) in *d*-chloroform was treated with lead(IV) tetraacetate and the reaction mixture was washed with sodium bicarbonate and filtered through silica. The ^{1}H NMR spectrum of this solution showed a range of products; signals representing the nitrile oxide (**81**) were singlets at δ2.09 (3H) and δ3.59 (4H). These signals are believed to correspond to the methyl and ring protons of the nitrile oxide (**81**), respectively. The parent compounds of the nitrile oxide (**81**), the aldehyde (**83**) and the oxime (**84**) show complex multiplets in their ^{1}H NMR spectra, representing their ring protons. The difference in the multiplicity of the ring proton signal in the spectrum of the nitrile oxide (**81**) compared to the ring proton signal in the spectra of the parent compounds (**83**) and (**84**), may be accounted for by a slight difference in 3-dimensional structure of the nitrile oxide (**81**). The nitrile oxide moiety is linear, compared to the aldehyde and oxime moieties which occupy a greater 2-D area. Comparison of intensity of the signals corresponding to the dithiolane ring protons of the nitrile oxide (**81**) compared to the signals of an internal standard (methyl benzoate) indicates a yield of approximately 10%, however the complexity of the spectrum precludes a more accurate calculation. The reason for the poor formation of the nitrile oxide (**81**) is likely to be similar to that for the lack of formation of the dithianenitrile oxide (**105**). The 2-methyl-1,3-dithiolanyl moiety has a smaller S-C-S bond angle than the 2-methyl-1,3-dithianyl moiety of the nitrile oxide (**104**),

resulting in a smaller effective steric bulk. The 2-methyl group provides more steric hindrance than the dithiane C2-proton in the nitrile oxide (**105**). The steric demands of the dithiolane ring therefore are such that the reactive conformation (**156a**), where R = 2-methyl-1,3-dithiolanyl, is formed less readily than the intermediate (**156a**) (R = 2-methyl-1,3-dithianyl) in the formation of the nitrile oxide (**104**), but more readily than the intermediate (**156a**) (R = 1,3-dithianyl) in the formation of the nitrile oxide (**105**).

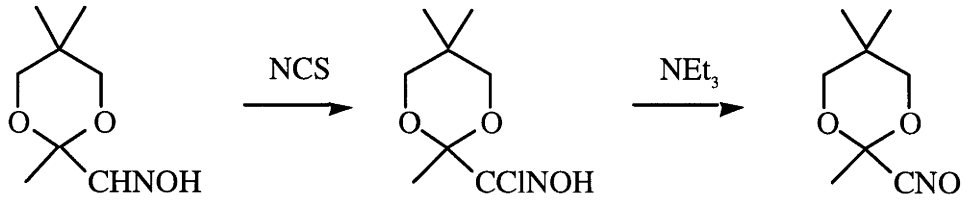
Due to the poor yield of synthesis of the nitrile oxide (**81**), IR spectroscopy was not practical.



(**158**)

The stability of the nitrile oxide (**81**) was studied by observation of its ^{1}H NMR spectrum over several hours. Comparison of both of the signal intensities of the nitrile oxide (**81**) with the intensity of the methyl ester signal of the internal standard, methyl benzoate, shows that approximately 10% of the nitrile oxide (**81**) remains in solution after 18 hrs, from an initial concentration of 0.02 M, from the initial nitrile oxide generation described above. The rapid decomposition at a lower concentration indicates that the dithiolanenitrile oxide (**81**) is considerably less stable than the dithianenitrile oxide (**104**). The reason for the difference in stability is unclear. It appears that the nitrile oxide (**81**) is not dimerising to the furoxan (**158**), but instead decomposing to an unknown product or mixture of products. While there is an increase in the intensity of a multiplet at δ3.3 - 3.5, there is no increase in the relative intensity of signals in the region δ1.5 - 2.5, where signals corresponding to the two methyl groups of the furoxan (**158**) would be expected.

5.3 2,5,5-Trimethyl-1,3-dioxane-2-carbonitrile N-*Oxide*



(143) **(159)** **(160)**

Scheme 49

The oxime (**143**) was treated with *N*-chlorosuccinimide in DMF to form the hydroximinoyl chloride (**159**) (Scheme 49).[129] However, since the oxime (**143**) is heat sensitive as mentioned in the previous chapter, it was necessary to keep the temperature below 20°C in order to prevent excessive decomposition. This results in inefficient conversion of the oxime (**143**) to the hydroximinoyl chloride (**159**). The unreacted starting material and its decomposition product were sufficiently volatile to remove by distillation. The hydroximinoyl chloride (**159**) was identified by the appearance of a broad singlet of variable chemical shift and intensity at δ7.5 - 8.5 in its ^{1}H NMR spectrum.

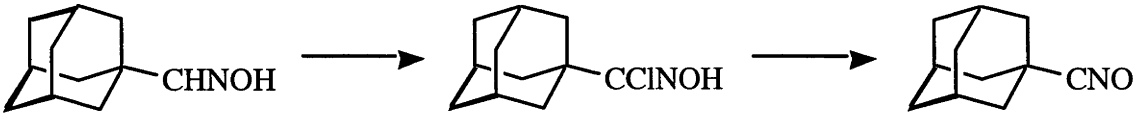
The nitrile oxide (**160**) was generated from the hydroximinoyl chloride (**159**) by elimination with triethylamine. The presence of the nitrile oxide (**160**) was confirmed using IR spectroscopy, which shows a characteristic nitrile oxide signal at 2260 cm^{-1}.

The stability of the nitrile oxide (**160**) was tested by observing the intensities of the signals in the ^{1}H NMR spectrum corresponding to the methyl groups at δ0.80, δ1.16 and δ1.79 compared to the intensities of the methyl ester signal at δ3.94 of an internal standard, methyl benzoate. The nitrile oxide (**160**) was generated quantitatively *in situ* from the hydroximinoyl chloride (**159**) in an NMR tube by addition of triethylamine. The nitrile oxide (**160**) was short-lived compared to the sulfur-containing analogue (**104**). After 24 hours, the quantity of nitrile oxide (**160**) in a sample of initial concentration 0.07 M had dropped to 10% of the initial amount present. A range of other signals was observed, however none could be identified as belonging to a dimer. Curiously, among the signals were observed those corresponding to the unidentified decomposition product of the oxime

(143), which were not present in the spectrum of the starting material. This suggests that the oxime **(143)** and nitrile oxide **(160)** may be decomposing *via* the same intermediate.

In order to determine if the presence of the triethylamine hydrochloride salt was affecting the stability of the nitrile oxide **(160)**, a slight modification of the procedure was investigated. A sample of the hydroximinoyl chloride **(143)** in *d*-chloroform was washed with saturated sodium bicarbonate solution. The organic solution was then dried and filtered through a plug of silica. The ^{1}H NMR spectrum of the filtrate shows the presence of signals corresponding to the desired nitrile oxide **(160)**. However, also present were the signals corresponding to the unknown decomposition product of the oxime **(143)**. After three days, the nitrile oxide **(160)** was no longer present according to the ^{1}H NMR spectrum. In addition, the number of other signals observed was reduced compared to the signals present when the nitrile oxide **(160)** was generated *via* elimination with triethylamine. It is clear that the nitrile oxide **(160)** is considerably less stable than its sulfur-containing analogue **(104)**. It is also apparent that the nitrile oxide **(160)** does not dimerise, instead decomposing to an unknown product or mixture of products.

5.4 Adamantanecarbonitrile N-*Oxide*



(146) **(161)** **(22)**

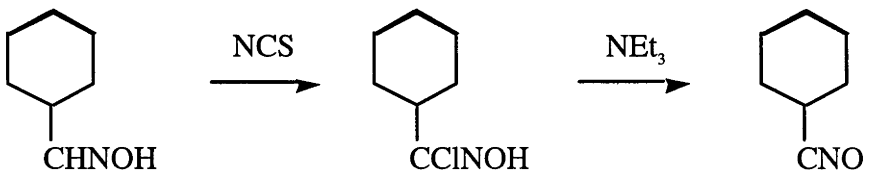
Scheme 50

The chlorooxime **(161)** was synthesised from the corresponding oxime **(146)** by treatment with *N*-chlorosuccinimide in DMF. Adamantanecarbonitrile *N*-oxide **(22)** was synthesised by elimination of hydrogen chloride from the hydroximinoyl chloride **(161)** (Scheme 50). The presence of the nitrile oxide was confirmed using IR spectroscopy. The nitrile oxide **(22)** shows a characteristic nitrile oxide signal at 2290 cm^{-1}.

The stability of the nitrile oxide could not be judged by ^{1}H NMR spectroscopy, since the nitrile oxide monomer (**22**) cannot be distinguished from the furoxan dimer (**25**) using this technique. Instead, the stability was investigated qualitatively by IR spectroscopy. A 0.25 M solution of the hydroximinoyl chloride (**161**) was treated with triethylamine. The IR spectrum of this solution was recorded at intervals over several days. The intensity of the C≡N absorbance at 2290 cm^{-1} was used as an indication of nitrile oxide concentration. The intensity of this absorbance decreased slowly over the course of a week. After 3 days at room temperature, the intensity of this absorbance was reduced by approximately 50%. After 6 days, only a trace of nitrile oxide was visible. Over the time period investigated, there was an increase in intensity of signals at 1500 (c/f lit:[50] 1550 cm^{-1} in CCl_4 – C_2H_4) and 1660 cm^{-1}, which are consistent with the formation of a strained furoxan.[60]

Taking into account the greater concentration, the stability of adamantanecarbonitrile *N*-oxide (**22**) is comparable to that of the dithianenitrile oxides (**104**) and (**106**), which was expected due to the similarities in steric bulk between these species.

5.5 Cyclohexanecarbonitrile N-*Oxide*

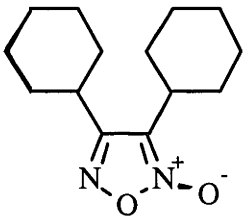


(148) **(162)** **(87)**

Scheme 51

Chlorocyclohexyl(hydroxyimino)methane (**162**) was synthesised by treatment of the corresponding oxime (**148**) with *N*-chlorosuccinimide in DMF (Scheme 51). The presence of the hydroximinoyl chloride (**162**) was indicated by the presence of a broad

signal at δ8.0 in the ^{1}H NMR spectrum. The hydroximinoyl chloride (**162**) was found to be unstable and it was necessary to use it immediately. Prolonged storage leads to decomposition to a white solid, which is insoluble in most solvents. The nitrile oxide (**87**) was generated from the chlorooxime (**162**) by elimination with triethylamine. The presence of the nitrile oxide (**87**) was confirmed by IR spectroscopy, which shows a characteristic nitrile oxide signal at 2302 cm^{-1}.



(163)

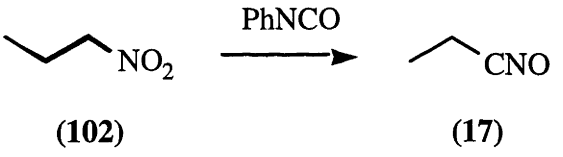
The nitrile oxide (**87**) was initially generated *in situ* in an NMR tube by treatment of the hydroximinoyl chloride (**162**) with triethylamine (Scheme 51). However, since the signal from the C1-proton at δ2.9 (1H, m) overlaps with the triethylamine signal at δ2.8, it is not possible to follow the decomposition of the nitrile oxide (**87**) directly by ^{1}H NMR when generated by this method. The signals in the ^{1}H NMR spectrum representing the rest of the protons in the molecule (C2-C6), at δ1.2 - 2.0, overlap significantly with those of the dimer (**163**). The appearance of the dimer (**163**) can be observed as a complex multiplet at δ2.2-δ2.3 in the ^{1}H NMR spectrum which represents the cyclohexane C-1 and C-1' protons. The dimer (**163**) was identified by mass spectroscopy, having a molecular ion at *m/z* 150.

The nitrile oxide (**87**) was generated by washing a solution containing the chlorooxime (**162**) with a saturated solution of sodium bicarbonate in order to follow its decomposition. This procedure gave a 70% yield of the nitrile oxide (**87**). By following the intensity of the signal at δ2.8 (C1-H, m) compared to that of the methyl ester signal of methyl benzoate, it was possible to calculate the half-life of the nitrile oxide (**87**) as approximately 3 days at room temperature from an initial concentration of 0.06 M.

The dimerisation of cyclohexanecarbonitrile *N*-oxide (**87**) was also examined by IR spectroscopy. After 28 hours at room temperature from an initial concentration of 0.24 M, the signal at 2302 cm^{-1} was no longer visible. As the initial rate of dimerisation was some 16 times more rapid in the IR study, the faster decomposition seen here is consistent with that seen in the ^1H NMR study.

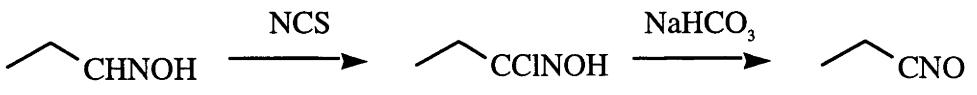
The shorter lifetime of cyclohexanecarbonitrile *N*-oxide (**87**) compared to adamantanecarbonitrile *N*-oxide (**22**) clearly shows the role of the increased steric bulk of the latter nitrile oxide in retarding dimerisation. At the same concentration and temperature, adamantanenitrile *N*-oxide (**22**) shows a considerably greater level of stability.

5.6 Propanenitrile N-*Oxide*



(102) **(17)**

Scheme 52



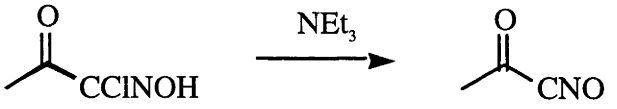
(150) **(164)** **(17)**

Scheme 53

Propanenitrile *N*-oxide (**17**) was generated by both dehydration of nitropropane (**102**) with phenyl isocyanate (Scheme 52) and elimination of 1-chloro-1-(hydroxyimino)propane (**164**) with base (Scheme 53). The hydroximinoyl chloride (**164**) was generated from hydroxyiminopropane (**150**) using *N*-chlorosuccinimide. 1-Chloro-1-(hydroxyimino)propane (**164**) was unstable at 4°C, and decomposed rapidly to give an unidentified white solid.

In order to measure stability, the propanenitrile *N*-oxide (**17**) was generated by washing a solution of the freshly prepared hydroximinoyl chloride (**164**) with saturated sodium bicarbonate. The nitrile oxide (**17**) dimerises such that approximately 50% remains in solution after 24 hours from an initial concentration of 0.08 M. None remains in solution after 5 days. This rate of dimerisation was somewhat faster than the dimerisation of cyclohexanecarbonitrile *N*-oxide (**87**), which was expected on the basis of their relative steric bulk. However, as the decomposition of alkylnitrile oxides is generally reported to be immeasurably rapid, the rate observed was unexpectedly slow. As the rate is also consistent with the rate observed by Mitchell and Paton[51] for ethanenitrile *N*-oxide (**16**), it would appear that primary alkylnitrile oxides are more stable than they are generally regarded. While the methyldithianenitrile oxide (**104**), an analogue of propanenitrile *N*-oxide (**17**), exhibits greater stability, the stability of the nitrile oxide (**17**) should be sufficient to allow a reasonable extent of cycloaddition to dipolarophiles.

5.7 2-Oxopropanenitrile N-*Oxide*

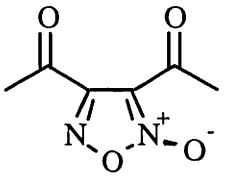


(151) **(61)**

Scheme 54

2-Oxopropanenitrile *N*-oxide (**61**) was generated *in situ* by elimination of hydrogen chloride from pyruvaldehyde-1-hydroximinoyl chloride (**151**) using triethylamine as a base (Scheme 54). The nitrile oxide (**61**) dimerises extremely rapidly to the bisacetylfuroxan (**165**). This dimerisation is complete within five minutes from an initial concentration of 0.08 M. The dimer (**165**) was identified by ^{1}H NMR and IR spectroscopy. The dimer (**165**) shows two singlets at δ2.62 and δ2.70 in the ^{1}H NMR spectrum, representing the non-equivalent 3- and 4-acyl substituents. The IR spectrum shows absorbances at 1800 and

1700 cm^{-1} (C=O), 1610 cm^{-1} (C=N-O) and 1490 cm^{-1} ($C=NO_2$). These data are consistent with those reported in the literature.[135] The dimer (**165**) is a yellow oil which decomposes on silica, making further purification impossible. The extreme rapidity of the dimerisation of 2-oxopropanenitrile *N*-oxide (**61**) was unexpected. In terms of steric bulk, the nitrile oxide is similar to nitrile oxides such as benzonitrile oxide (**3**) (a nitrile oxide with an adjacent sp^2-hybridised centre), which has a lifetime of several days from a 0.1 M solution,[49] or propanenitrile *N*-oxide (**17**) (a primary alkylnitrile oxide) which has a half life of 24 hours from a 0.08 M solution. Obviously, the rapid dimerisation of the nitrile oxide (**61**) must be related to its electronic structure.



(165)

The dithiane moiety of the nitrile oxide (**104**) allows this species to act as a masked form of the nitrile oxide (**61**). The effect of this moiety on the stability of the nitrile oxide (**104**) relative to the stability of the nitrile oxide (**61**) is profound. The methyldithianenitrile oxide (**104**) has a half-life of 8 days in solution at a concentration of 0.05 M. The acetylnitrile oxide (**61**) in contrast dimerises immediately at 0.08 M. The dimerisation of the acetylnitrile oxide (**61**) is likely to be too rapid to allow a large degree of cycloaddition to dipolarophiles.

5.8 Summary

The effect of steric bulk on the lifetime of alkylnitrile oxides can be seen by comparison of the primary, secondary and tertiary alkylnitrile oxides (**17**), (**87**) and (**22**). The smaller primary nitrile oxide dimerises more rapidly than the secondary nitrile oxide, which in turn dimerises more rapidly than the tertiary. This trend is also represented in the dithianenitrile oxides, with the sterically more hindered 2-butyl-1,3-dithiane-2-carbonitrile

N-oxide (**106**) showing more stability than 2-methyl-1,3-dithiane-2-carbonitrile *N*-oxide (**104**) under similar conditions.

Both the dithiolanenitrile oxide (**81**) and the dioxanenitrile oxide (**160**) show reduced stability compared to the dithianenitrile oxides (**104**) and (**106**). Neither the dithiolanenitrile oxide (**81**) nor the dioxanenitrile oxide (**160**) appear to dimerise, but rather decompose *via* unknown routes.

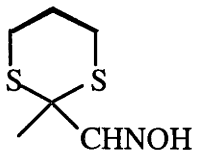
The extremely rapid dimerisation of the nitrile oxide (**61**) appears to result from electronic effects rather than steric effects. The contribution of the electron-withdrawing carbonyl group appears to facilitate the dimerisation.

2-Methyl-1,3-dithiane-2-carbonitrile *N*-oxide (**104**) has a greater lifetime in solution than either propanenitrile *N*-oxide (**17**) or 2-oxopropanenitrile *N*-oxide (**61**). Therefore, the dithiane moiety of nitrile oxide (**104**) allows this compound to act as a more stable analogue of the nitrile oxides (**17**) and (**61**). Similarly, 2-butyl-1,3-dithiane-2-carbonitrile *N*-oxide (**106**) can be expected to act as a longer-lived analogue of longer chain alkyl- and acyl-nitrile oxides. The use of the methyldithianenitrile oxide (**104**) as a steric auxiliary is likely to be more important for the extremely unstable nitrile oxide (**61**) than with the nitrile oxide (**17**), as the nitrile oxide (**17**) is expected to be sufficiently stable to allow a reasonable level of activity towards dipolarophiles, while the nitrile oxide (**61**) is not.

Chapter 6: Results and Discussion – 1,3-Dithiane-2-Carbonitrile *N*-Oxides as Steric Auxiliaries

The dithianenitrile oxides (**104**) and (**106**), the dithiolanenitrile oxide (**81**), the dioxanenitrile oxide (**160**), the alkylnitrile oxides (**17**), (**22**), and (**87**) and the acylnitrile oxide (**61**) were generated from their precursors as described in Chapter 5. Their cycloadditions were investigated in order to determine the extent to which their stability affects their reactivity with alkenes. It was expected that the greater stability of 2-methyl-1,3-dithiane-2-carbonitrile *N*-oxide (**104**), 2-butyl-1,3-dithiane-2-carbonitrile *N*-oxide (**106**) and adamantanecarbonitrile *N*-oxide (**22**) would allow a greater extent of cycloaddition to dipolarophiles than that of the cycloadditions of the shorter-lived nitrile oxides.

6.1 1,3-Dithiane-2-carbonitrile N-*Oxides*

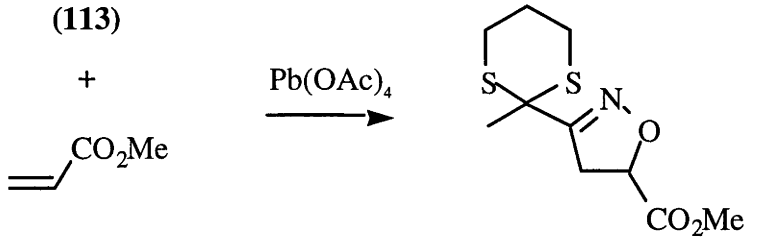


(**113**)

(**104**)

2-Methyl-1,3-dithiane-2-carbonitrile *N*-oxide (**104**) was generated from the oxime (**113**) as described in section 5.1. The nitrile oxide (**104**) was treated with a range of dipolarophiles and the adducts were isolated and characterised. In addition, ^{1}H NMR experiments were carried out in order to determine the crude yield of cycloaddition. These experiments consisted of treating samples of a 0.05 M stock solution of the nitrile oxide (**104**) with a range of dipolarophiles in the presence of methyl benzoate as an internal standard. The yield of each cycloaddition product was calculated by comparison of the

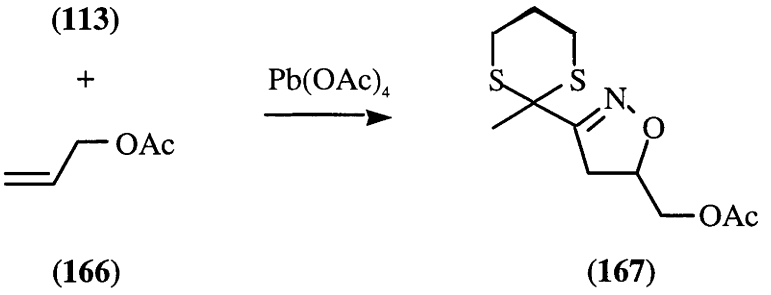
signal intensities of the isoxazoline signals in the ^{1}H NMR spectrum with the intensity of the methyl ester resonance of the internal standard.



(34) **(155)**

Scheme 55

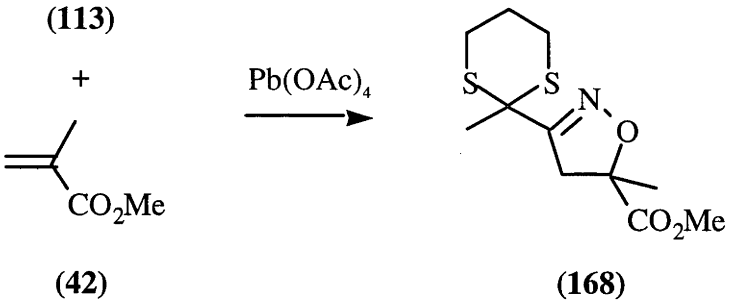
The treatment of the oxime **(113)** with lead(IV) tetraacetate in the presence of methyl acrylate **(34)** proceeded to afford the isoxazoline **(155)** (Scheme 55). The isolated yield was 55%. The ^{1}H NMR study showed that the cycloaddition to methyl acrylate **(34)** was comparatively rapid; the reaction was complete (*i.e.*, no further change in ^{1}H NMR spectrum) in less than two hours, compared with more than two weeks for the decomposition of the nitrile oxide **(104)**. This study showed that the crude yield of the isoxazoline **(155)** was 83% from the nitrile oxide **(104)**. The isoxazoline **(155)** was identified using its ^{1}H NMR spectrum. A doublet of doublets at δ5.03 (1H) represents the C5-proton, and an ABX multiplet at δ3.3 - δ3.4 (2H) represents the C4-protons. These ^{1}H NMR data are consistent with those of similar compounds presented in the literature; the chemical shift of the 4- and 5-protons in 5-methoxycarbonylisoxazolines shows little variation with the C3-substituent.[78] The 4- and 5-protons of 4-methoxycarbonylisoxazolines give ^{1}H NMR signals in the region δ4.1 - 4.8. The 5-methoxycarbonyl isomer **(155)** was the only isomer detected.



(166) (167)

Scheme 56

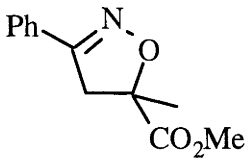
The treatment of the oxime (**113**) with lead(IV) tetraacetate in the presence of allyl acetate (**166**) gave the isoxazoline (**167**) (Scheme 56). The isolated yield was 40% from the oxime (**113**). The ^{1}H NMR study carried out as described above showed that the reaction required a longer time to go to completion than the cycloaddition of the nitrile oxide (**104**) to methyl acrylate (**34**) (five hours before no further change in ^{1}H NMR signal intensity was observed). This may be because allyl acetate (**166**) is less activated towards cycloaddition, due to the lack of polarisation of the double bond; as described in the introduction, an electron withdrawing and conjugating group will favour a 1,3-dipolar cycloaddition. This study gave the crude yield of cycloaddition of the nitrile oxide (**104**) to allyl acetate (**166**) as 85%. The isoxazoline (**167**) was identified using its ^{1}H NMR spectrum. This spectrum shows a multiplet at δ4.90 (1H) representing the C5-proton, and two separate sets of doublets of doublets (1H each) which represent the C4-protons. The first of these is at approximately δ3.25, and is partially obscured by the multiplet caused by one of the equatorial protons of the methylene groups adjacent to sulfur, while the second is at δ2.96. These ^{1}H NMR data are consistent with the isoxazoline resonances presented in the literature for a similar compound, 5-methyl-3-phenyl-4,5-dihydroisoxazole (δ4.84, dd (sic), δ3.38, dd, and δ2.88, dd).[136] As with the cycloaddition of the nitrile oxide (**104**) to methyl acrylate (**34**), only the 5-substituted regioisomer (**167**) was detected. The 4-substituted isomer would be expected to show the multiplet corresponding to methine at a lower chemical shift, reflecting the smaller deshielding effect of the C=N group compared to the 1-oxygen.



(42) (168)

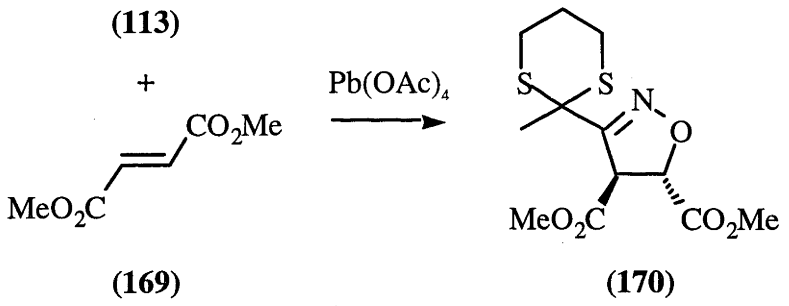
Scheme 57

The treatment of the oxime (**113**) with lead(IV) tetraacetate in the presence of the 1,1-disubstituted alkene methyl methacrylate(**42**) gave the isoxazoline (**168**) (Scheme 57). The isolated yield was 28%. The isolated yield of the cycloaddition of the nitrile oxide (**104**) to the 1,1-disubstituted alkene methyl methacrylate(**42**) was somewhat lower than that to the monosubstituted analogue, methyl acrylate (**34**); this relates to poor separation of the isoxazoline (**168**) from reaction byproducts using flash chromatography. The ^{1}H NMR study of the reaction of the nitrile oxide (**104**) with methyl methacrylate(**42**) gave a crude yield of cycloaddition of 80% from the nitrile oxide (**104**), comparable to the crude yield of cycloaddition of the nitrile oxide (**104**) to methyl acrylate (**34**). This indicates that the added steric bulk on the dipolarophile in the 1-position does not affect the efficiency of the cycloaddition. Only one regioisomer was detected, the 5-methoxycarbonyl-5-methylisoxazoline (**168**), which was identified using its ^{1}H NMR spectrum. Doublets at δ3.62 and δ2.98 represent the C4-protons, showing strong geminal coupling to each other (J = 17 Hz). While there is no C5-proton, the C4-proton resonances are consistent with those of a similar compound, methyl 5-methyl-3-phenylisoxazoline-5-carboxylate (**44**) (δ3.83, d, δ3.21, d, J = 17.5 Hz).[136] This difference results from the deshielding effect of the carbonyl group on the proton *cis* to this proton.[78] The alternate regioisomer would be expected to show resonances at a higher chemical shift to reflect the proximity of the protons to the 1-oxygen, by analogy with 4-methoxycarbonylisoxazolines, which show C5-proton resonances at δ4.5 - 4.8.[78]



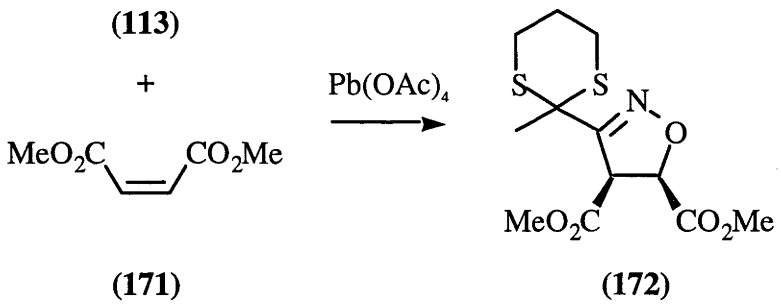
(44)

Cycloadditions of the nitrile oxide (**104**) to 1,2-disubstituted alkenes were considerably slower than those to mono-substituted alkenes. These reactions were each given a two-day reaction time, after which point no further change in the ^{1}H NMR spectrum was observed. This rate of reaction is still considerably greater than the rate of decomposition of the nitrile oxide (**104**).



(113) + **(169)** → **(170)**

Scheme 58

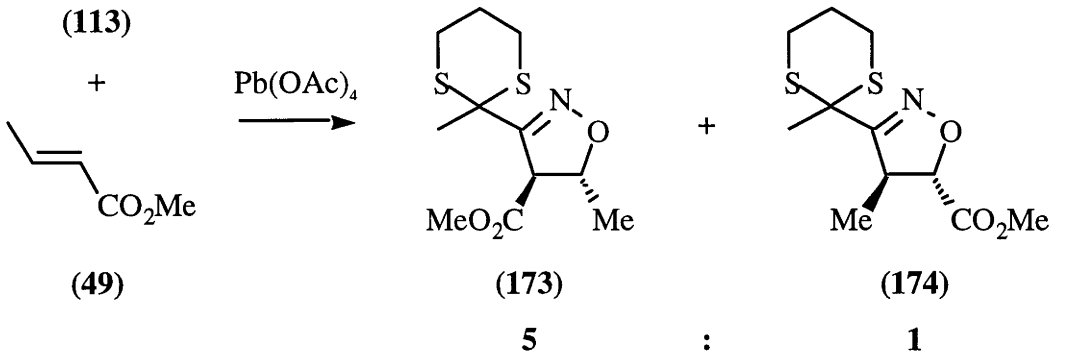


(113) + **(171)** → **(172)**

Scheme 59

The treatment of the oxime (**113**) with lead(IV) tetraacetate in the presence of dimethyl fumarate (**169**) gave the cycloadduct (**170**) in an isolated yield of 64% (Scheme 58), which is somewhat higher than expected when compared to the yields of cycloadditions to the monosubstituted alkenes described above. The treatment of the oxime (**113**) with lead(IV) tetraacetate in the presence of dimethyl maleate (**171**) (Scheme 59) gave the cycloadduct (**172**) in an isolated yield of 44%. The difference in yield appears to

be due to the poorer isolation of the isoxazoline (**172**); the ^{1}H NMR studies, carried out as described above, show a yield of the cycloadduct (**170**) of 78% from the nitrile oxide (**104**), and a yield of the cycloadduct (**172**) of 73% from the nitrile oxide (**104**). Both dimethyl fumarate (**169**) and dimethyl maleate (**171**) are highly active towards cycloaddition due to the highly conjugated nature of the double bond, in accordance with Sustmann's model for cycloaddition described in the introduction. The products of the reaction were identified using their ^{1}H NMR spectra. The ^{1}H NMR spectrum of the adduct (**170**) shows doublets at δ5.31 and δ4.44, corresponding to the C5-proton and C4-proton respectively. The ^{1}H NMR spectrum of the adduct (**172**) shows doublets at δ5.29 and δ4.34, corresponding to the C5-proton and C4-proton respectively. Although the chemical shifts of these isomers are very similar, the coupling constants between the C4- and C5-protons of the two diastereoisomers show a considerable difference in magnitude. The coupling constant in the 4,5-*trans*-substituted isoxazoline (**170**) is 5 Hz, while the coupling constant in the 4,5-*cis*-substituted isoxazoline (**172**) is 11 Hz. The ^{1}H NMR shift and coupling data of these compounds are consistent with the data in the literature for the 3-phenyl analogues of these compounds.[136] The difference in magnitude of the coupling constants is accounted for by the Karplus equation.[137] The Karplus equation states that a larger coupling constant is observed when the dihedral angle between protons approaches either 0°, which is expected in the isoxazoline protons of the 4,5-*cis*-isoxazoline (**172**), or 180°. The Karplus equation predicts a smaller coupling constant as the dihedral angle approaches 90°. The isoxazoline protons of the 4,5-*trans*-isoxazoline (**170**) would be expected to have a greater dihedral angle than those of the 4,5-*cis*-isoxazoline (**172**) due to the constrained nature of the isoxazoline ring, resulting in the smaller coupling constant. Only one stereoisomer is observed in each case, which is consistent with the cycloaddition proceeding with retention of stereochemistry.[62, 63]



(49) (173) (174)

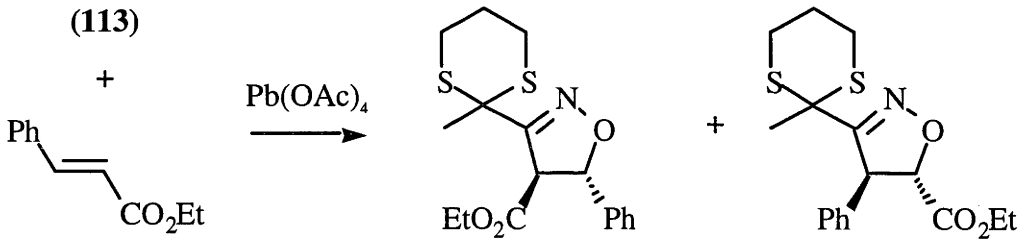
5 : 1

Scheme 60

Cycloadditions of the nitrile oxide **(104)** to asymmetric substituted alkenes result in mixtures of isomeric isoxazolines. The treatment of the oxime **(113)** with lead(IV) tetraacetate in the presence of methyl crotonate **(49)** (Scheme 60) proceeds to form the isoxazolines **(173)** and **(174)**. The isolated yield of the 4-methoxycarbonylisoxazoline **(173)** was 33% from the oxime **(113)**. The 5-methoxycarbonyl isomer **(174)** was isolated in a yield of < 2%. The low yield of the minor isomer **(174)** was due to poor separation from the major isomer **(173)**; a small level of contamination from the major isomer could be removed from the minor isomer only with difficulty. The cycloaddition of the nitrile oxide **(104)** to methyl crotonate **(49)** gives a 5:1 mixture of the regioisomers **(173)** and **(174)** (Scheme 60), in a reasonable yield. The ^{1}H NMR study, carried out as described above, showed that the reaction proceeded to give a combined yield of both isomers **(173)** and **(174)** of 58% from the nitrile oxide **(104)**, in a ratio of 5:1. The isomers were identified using ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of the minor isomer **(174)** shows a doublet at δ4.66 (1H) and a doublet of quartets at δ3.64 (1H). The splitting pattern of the lower field signal indicates that it represents the α-carbonyl proton, as it is not coupled to a methyl group, and the high chemical shift indicates the proximity of the 1-oxygen. The splitting pattern of the higher field signal indicates the proximity of a methyl group. The ^{1}H NMR spectrum of the major isomer **(173)** shows an apparent pentet at δ4.98 and a doublet at δ3.71. The lower field signal was assigned as proximal to the oxygen atom, and the multiplicity is consistent with an adjacent methyl group. Only two

isomers are observed in this case, which is expected if the reaction proceeds with retention of stereochemistry.[62, 63]

The regiochemistry of the cycloaddition of 2-methyl-1,3-dithiane-2-carbonitrile *N*-oxide (**104**) to methyl crotonate (**49**) is similar to that shown by 2,2-dimethylpropanenitrile *N*-oxide (**18**), which is consistent with the similar steric requirements between the *t*-butyl and methyldithiane moieties.[78]



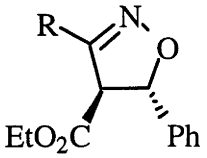
(70) **(175)** **(176)**

4 : **1**

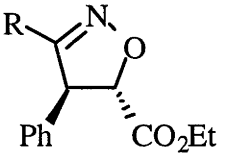
Scheme 61

The treatment of the oxime (**113**) with lead(IV) tetraacetate in the presence of ethyl cinnamate (**70**) gives the isoxazolines (**175**) and (**176**) (Scheme 61). The isolated yield of the 4-ethoxycarbonylisoxazoline (**175**) was 49% from the oxime (**113**). The 5-ethoxycarbonylisoxazoline (**176**) was isolated in a yield of < 5%. The low yield of the minor isomer (**176**) was due to poor separation from the major isomer (**175**); a small level of contamination from the major isomer could be removed from the minor isomer only with difficulty. The ^{1}H NMR study showed that the reaction proceeded in a total yield of 56% for both isomers from the nitrile oxide (**104**), in a ratio of 4:1. Only two isomers are observed in this case, which is expected if the reaction proceeds with retention of stereochemistry.[62, 63] These isomers were identified using their ^{1}H NMR spectra. The ^{1}H NMR spectrum of the major isomer (**175**) shows a doublet at δ5.90 and a doublet at δ4.08, which are assigned as C5-H and C4-H, respectively. The high chemical shift of the C5-proton results from the combined deshielding effects of the adjacent phenyl moiety and the adjacent oxygen. The ^{1}H NMR spectrum of the minor isomer (**176**) shows a doublet at

δ4.90 and a doublet at δ4.72. Of these two signals, that with the higher shift is assigned as the C5-proton, due to the proximity of the oxygen, with the lower being assigned to the C4-proton. In the literature,[78, 136] the 4- and 5-protons of 4-methoxycarbonyl-5-phenylisoxazolines **(177)** consistently show a considerably greater difference in chemical shift than that between the signals of the 4- and 5-protons of 5-methoxycarbonyl-4-phenylisoxazolines **(178)**. The chemical shifts of the 4- and 5-protons of the isoxazolines **(175)** and **(176)** are consistent with this trend.

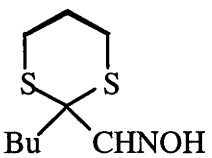


(177)

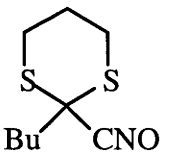


(178)

The regioselectivity observed in the cycloaddition of 2-methyl-1,3-dithiane-2-carbonitrile *N*-oxide **(104)** to ethyl cinnamate **(70)** is similar to that observed with 2,2-dimethylpropanenitrile *N*-oxide **(18)** to methyl cinnamate **(45)**, which is expected due to their similar steric bulk.

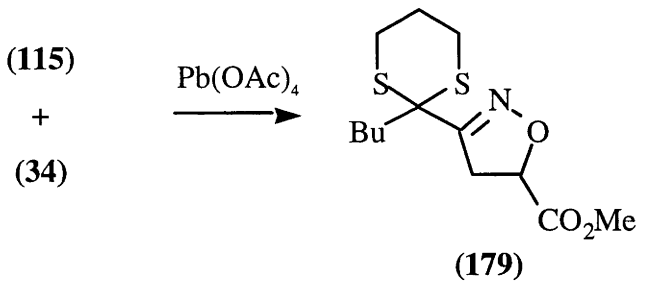


(115)



(106)

2-Butyl-1,3-dithiane-2-carbonitrile *N*-oxide **(106)** has been shown to have a longer lifetime in solution than 2-methyl-1,3-dithiane-2-carbonitrile *N*-oxide **(104)** (section 5.1). However, the half-lives of the methyldithianenitrile oxide **(104)** ($t_{1/2}$ = 8 days) and the butyldithianenitrile oxide **(106)** ($t_{1/2}$ > 6 weeks) are longer than the expected time of cycloaddition ($t_{1/2}$ ≈ 30 min for monosubstituted alkenes, $t_{1/2}$ ≈ 10 - 12 hours for disubstituted alkenes). Therefore, the difference in stability was not expected to have much influence on the outcome of the cycloadditions.



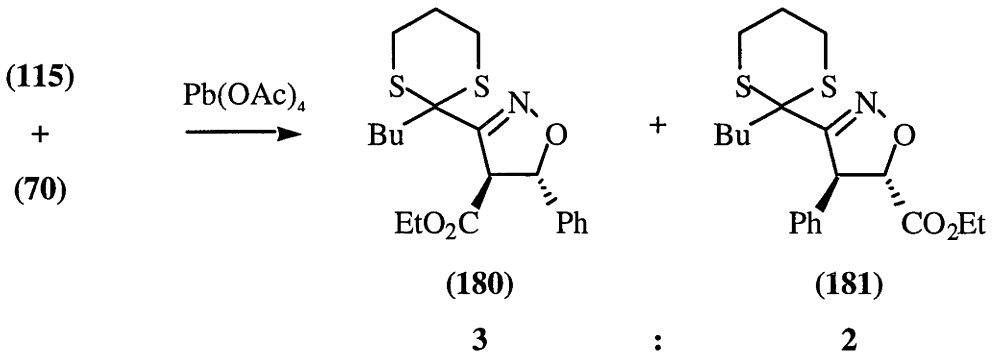
(179)

Scheme 62

Treatment of 2-butyl-1,3-dithiane-2-carboxaldehyde oxime **(115)** with lead(IV) tetraacetate in the presence of methyl acrylate **(34)** gave an isolated yield of the isoxazoline **(179)** of 25% (Scheme 62). The poor yield appears to be the result of poor formation of the nitrile oxide **(106)** and poor separation from the product mixture. The isoxazoline **(179)** shows similar C4- and C5-signals in the ^{1}H NMR spectrum to those of the 2-methyldithiane derived analogue **(155)**. A doublet of doublets at δ5.11 (1H) corresponds to the C5-proton, while an ABX multiplet at δ3.37 (2H) represents the C4-protons. The intensity, multiplicity and the high chemical shift of the signal at δ5.11 are all consistent with the assignment of this signal as the C5-proton of a 5-methoxycarbonylisoxazoline, by comparison with the ^{1}H NMR data of similar compounds in the literature.[78] As with the cycloaddition of the methyldithianenitrile oxide **(104)** to methyl acrylate **(34)**, the cycloaddition of butyldithianenitrile oxide **(106)** gives only one observed regioisomer, consistent with the general trends of cycloadditions to monosubstituted alkenes.

The extent of cycloaddition of the nitrile oxide **(106)** to methyl acrylate **(34)** was determined by creating a solution of the nitrile oxide **(106)** and treating it with the dipolarophile in an NMR tube in the presence of an internal standard, methyl benzoate, and recording ^{1}H NMR spectra of this reaction mixture regularly over 3 days. The extent of cycloaddition was then calculated by comparison of the signal intensities of the isoxazoline resonances of the cycloadduct **(179)** with those of the methyl ester resonance of the internal standard. This showed a crude yield of 86%, compared to 83% for the cycloaddition of methyldithianenitrile oxide **(104)**. This yield was based on the assumed yield of **(106)** of

43% from the oxime (**115**). The cycloaddition of the nitrile oxide (**106**) to methyl acrylate (**34**) proceeded slowly, with no further change in ^{1}H NMR spectrum after 24 hours. However, the cycloaddition of the nitrile oxide (**106**) to methyl acrylate (**34**) was rapid compared to its decomposition, which takes several weeks.



(**180**) : (**181**)

3 : 2

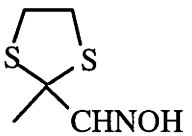
Scheme 63

The treatment of the oxime (**115**) with lead(IV) tetraacetate in the presence of ethyl cinnamate (**70**) gave a mixture of the isomers (**180**) and (**181**) (Scheme 63). The major isomer (**180**) was isolated in a yield of 10% and the minor isomer (**181**) in a yield of 1%. The poor yield appears to be the result of poor formation of the nitrile oxide (**106**) from the parent oxime (**115**), as well as poor separation of the isomers. The isomers (**180**) and (**181**) were identified using their ^{1}H NMR spectra. The ^{1}H NMR spectrum of the major isomer (**180**) shows two sets of doublets at δ5.95 and δ4.81, which are assigned as C5-H and C4-H, respectively. The assignment of the C5-proton is based on the high chemical shift of the signal, which results from the combined deshielding effects of the adjacent phenyl moiety and the adjacent oxygen. The ^{1}H NMR spectrum of the minor isomer (**181**) shows two sets of doublets at δ5.02 and δ4.80. The signal with the higher shift is assigned as the C5-proton, due to the proximity of the oxygen atom, with the lower being assigned to the C4-proton. These assignments are consistent with those of similar compounds in the literature.[78] As with the cycloaddition of the nitrile oxide (**104**) to ethyl cinnamate (**70**), only two isomers are observed in this case. This is consistent with the reaction proceeding with retention of stereochemistry.

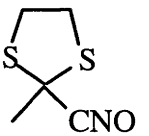
The extent of cycloaddition of the nitrile oxide (**106**) to ethyl cinnamate (**70**) was determined by creating a solution of the nitrile oxide (**106**) and treating it with the dipolarophile in an NMR tube in the presence of an internal standard, methyl benzoate, and recording ^{1}H NMR spectra of this reaction mixture regularly over 6 days, after which time no further change in signal intensity was observed. The extent of cycloaddition was then calculated by comparison of the signal intensities of the isoxazoline resonances of the cycloadduct (**179**) with those of the methyl ester resonance of the internal standard, methyl benzoate. The cycloaddition gives a mixture of the isomers (**180**) and (**181**) in the ratio of 3:2. This gave a crude yield of 80% from the nitrile oxide (**106**), compared to 56% for the cycloaddition if the methyldithianenitrile oxide (**104**) to ethyl cinnamate (**70**).

The nitrile oxides (**104**) and (**106**) undergo cycloaddition to alkenes as expected from their half-lives and the expected time for cycloadditions. The half-life of dimerisation in both cases is considerably longer than the half-life of cycloaddition, thus allowing a large extent of cycloaddition.

6.2 2-Methyl-1,3-dithiolane-2-carbonitrile N-*Oxide*



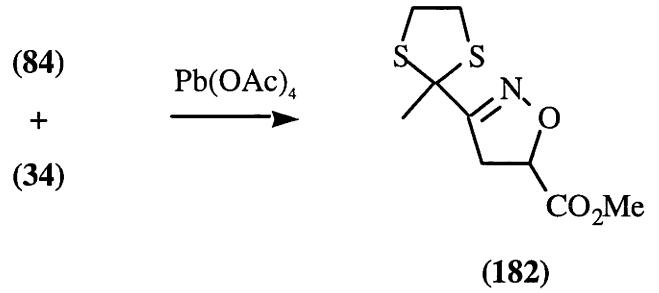
(**84**)



(**81**)

As described in section 0, 2-methyl-1,3-dithiolane-2-carbonitrile *N*-oxide (**81**) has a considerably shorter lifetime than 2-methyl-1,3-dithiane-2-carbonitrile *N*-oxide (**104**). The smaller steric bulk of the nitrile oxide (**81**) would be expected to result in a slightly more rapid rate of cycloaddition to alkenes than that of the methyldithianenitrile oxide (**104**). However, the rate of decomposition of the nitrile oxide (**81**), with a half-life of approximately 6 hours from a concentration of 0.02 M, was expected to be considerably

faster than the rate of cycloaddition to disubstituted alkenes, with an expected half-life of around 10 - 12 hours. Therefore, the nitrile oxide (**81**) was expected to show a poorer extent of cycloaddition to disubstituted alkenes than the methyldithianenitrile oxide (**104**). Cycloaddition to monosubstituted alkenes, with a half-life of around 30 minutes, was expected to be unaffected.

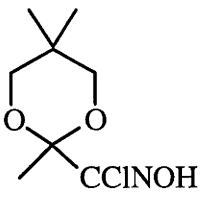


(182)

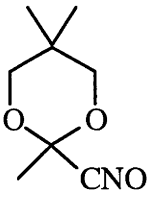
Scheme 64

Treatment of 2-methyl-1,3-dithiolane-2-carboxaldehyde oxime (**84**) with lead(IV) tetraacetate in the presence of methyl acrylate (**34**) as a dipolarophile resulted in the formation of methyl 3-(2-methyl-1,3-dithiolan-2-yl)-4,5-dihydroisoxazole-5-carboxylate (**182**) in 15% yield (Scheme 64). The poor yield is due to the poor formation of the nitrile oxide (**81**) from the oxime (**84**), discussed in section 0. The isoxazoline (**182**) was found to be unstable, and decomposed to a brown oil on standing at room temperature. The ^{1}H NMR spectrum of the isoxazoline (**182**) shows signals characteristic of a 5-methoxycarbonylisoxazoline at δ5.09 (1H, dd, C5-H), and δ3.58 (2H, ABX multiplet, C4-H_2). Due to the poor yield of formation of the nitrile oxide (**81**) from the oxime (**84**), the ^{1}H NMR cycloaddition studies described for the dithiane nitrile oxides (**104**) and (**106**) were not carried out.

6.3 2,5,5-Trimethyl-1,3-dioxane-2-carbonitrile N-*Oxide*

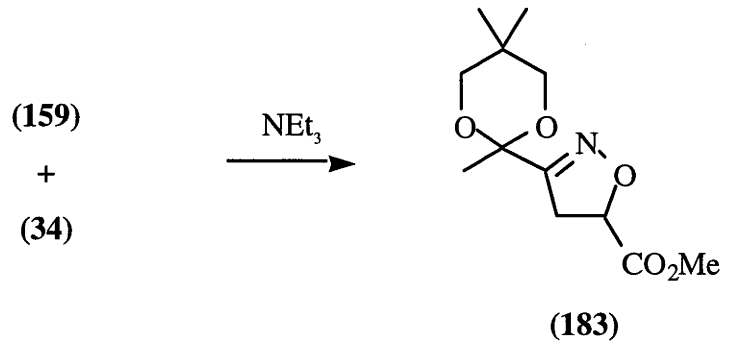


(159)



(160)

As described in section 5.3, 2,5,5-trimethyl-1,3-dioxane-2-carbonitrile *N*-oxide (**160**) has lower stability than the methyldithianenitrile oxide (**104**). Cycloaddition reactions of the nitrile oxide (**160**) with methyl acrylate (**34**), methyl crotonate (**49**) and ethyl cinnamate (**70**) were investigated. A 0.7 M solution of the nitrile oxide (**160**) was generated *in situ* from the hydroximinoyl chloride (**159**) by addition of triethylamine, in the presence of a dipolarophile and methyl benzoate as an internal standard. The progress of the reaction was observed over several days by ^{1}H NMR spectroscopy, with the extent of cycloaddition determined by comparison of the intensities of the isoxazoline resonances of the cycloadducts and the methyl ester resonance of the internal standard. The adducts of the nitrile oxide (**160**) were not isolated but were identified by analogy with similar compounds in the literature.[78]

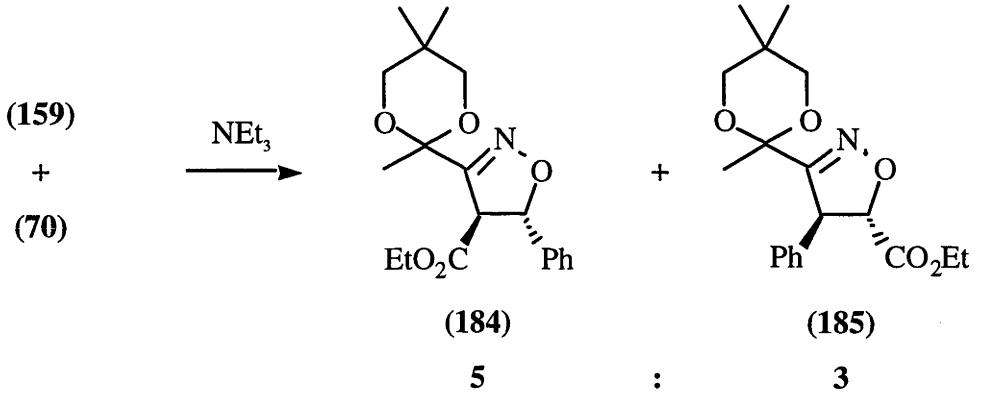


(183)

Scheme 65

Treatment of the hydroximinoyl chloride (**159**) with triethylamine in the presence of methyl acrylate (**34**) gave the isoxazoline (**183**) in a yield of 94% (Scheme 65). The isoxazoline (**183**) was identified using characteristic resonances in the ^{1}H NMR spectrum.

Signals at δ5.04 (triplet, 1H) and δ3.54 (doublet, 2H), representing the C5- and C4-protons respectively, are consistent with those of the isoxazoline protons of 5-methoxycarbonylisoxazolines presented in the literature.[78] The splitting pattern shown here is quite unusual, with no discrimination observed between the C4-protons at all, resulting in a simple AX_2 spin system, rather than the ABX system which is common for 3,5-disubstituted isoxazolines.[78, 138] No ^{1}H NMR signals in the region δ4.1 - 4.8, which would indicate the formation of the 4-methoxycarbonyl isomer, were observed.



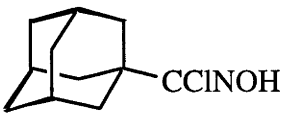
Scheme 66

Treatment of the hydroximinoyl chloride **(159)** with triethylamine in the presence of ethyl cinnamate **(70)** gave a mixture of the isoxazolines **(184)** and **(185)** in a yield of < 10% (Scheme 66). The ^{1}H NMR signals representing the isoxazolines **(184)** and **(185)** were barely visible above the baseline of the spectrum. For this reason, the calculations of yields and regioisomer ratio may not be accurate. The isoxazoline resonances in the ^{1}H NMR spectrum that were investigated were at δ5.63 and δ4.46 (C5-H and C4-H_2 of the major isomer **(184)**), and δ4.98 and δ4.52 (C5-H and C4-H_2 of the minor isomer **(185)**).

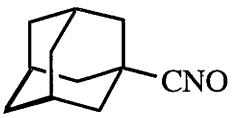
The lack of reactivity of the nitrile oxide **(160)** towards ethyl cinnamate **(70)**, compared to the cycloaddition of the dithiane analogue **(104)**, is believed to result from its comparatively low stability. The nitrile oxide **(160)** has a half-life of approximately 6 - 8 hours, while the half-life of the cycloaddition to ethyl cinnamate **(70)** was expected to be of the order of 10 - 12 hours, based on the corresponding reaction of the dithiane analogue

(**104**). The reaction of the nitrile oxide (**160**) with the monosubstituted alkene, methyl acrylate (**34**), proceeds in good yield as the cycloaddition is more rapid ($t_{1/2} \approx 30$ min) than the decomposition of the nitrile oxide (**160**).

6.4 Adamantanecarbonitrile N-*Oxide*



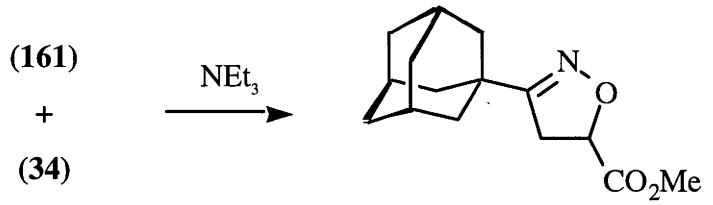
(**161**)



(**22**)

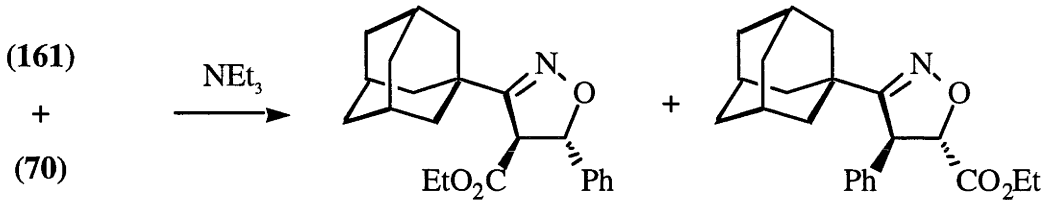
The cycloadditions of adamantanecarbonitrile *N*-oxide (**22**) to methyl acrylate (**34**) and ethyl cinnamate (**70**) were investigated. The nitrile oxide (**22**) has a half-life of 3 days at a concentration of 0.24 M. The similar steric bulk of adamantanecarbonitrile *N*-oxide (**22**) to the methyldithianenitrile oxide (**104**) was expected to result in similar reactivity towards dipolarophiles, with a half-life of approximately 30 minutes for monosubstituted alkenes and 10 - 12 hours for disubstituted alkenes. A 0.08 M solution of adamantanylchloro(hydroxyimino)methane (**161**) was treated with triethylamine in the presence of a dipolarophile and an internal standard. The cycloadducts of adamantanecarbonitrile *N*-oxide (**22**) described in this section were not isolated but were identified by analogy with similar compounds in the literature.[78]

Treatment of the hydroximinoyl chloride (**161**) with triethylamine in the presence of the monosubstituted dipolarophile methyl acrylate (**34**) gave the isoxazoline (**186**) in a yield of 59% (Scheme 67). The isoxazoline (**186**) was identified using characteristic resonances in the ^{1}H NMR spectrum. Signals at δ4.93 (dd, 1H) and δ3.20 (ABX multiplet, 2H) represent the C5- and C4-protons, respectively. The chemical shifts, intensities and splitting patterns of these signals are characteristic of a 5-methoxycarbonylisoxazoline.[78]



(186)

Scheme 67



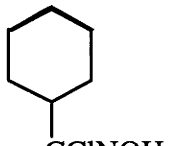
(187) **(188)**

3.8 : **1**

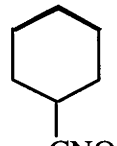
Scheme 68

Treatment of the hydroximinoyl chloride (**161**) with triethylamine in the presence of the 1,2-disubstituted dipolarophile ethyl cinnamate (**70**) (Scheme 68) gave a mixture of the isoxazolines (**187**) and (**188**) in a combined yield of 36%, in a ratio of 3.8:1. The reaction took approximately two days before no further change was observed in the ^{1}H NMR spectrum. The isoxazoline resonances in the ^{1}H NMR spectrum that were investigated were at δ5.66 and δ3.93 (C5-H and C4-H_2 of the major isomer (**187**)), and δ4.69 and δ4.52 (C5-H and C4-H_2 of the minor isomer (**188**)). The ratio of regioisomers is almost identical to that observed with 2,2-dimethylpropanenitrile *N*-oxide (**18**) to methyl cinnamate (**45**).[78] The ratio was also similar to that observed in the cycloaddition of methyldithianenitrile oxide (**104**) to ethyl cinnamate (**70**). The similarities in regioselectivity among these nitrile oxides is expected due to similarities in steric nature.

6.5 Cyclohexanecarbonitrile N-*Oxide*

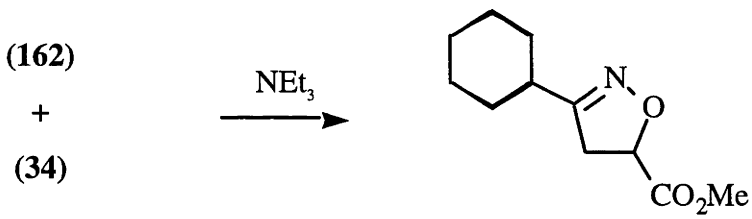


(162)



(87)

The cycloadditions of cyclohexanecarbonitrile *N*-oxide (**87**) to methyl acrylate (**34**), methyl crotonate (**49**) and ethyl cinnamate (**70**) were investigated. The nitrile oxide (**87**) has a half-life of approximately 3 days at a concentration of 0.06 M. The half-life of dimerisation of the nitrile oxide (**87**) is larger than the expected half-life of cycloaddition to alkenes, which should allow a good extent of cycloaddition. The nitrile oxide (**87**) was generated *in situ* at a concentration of 0.08 M from the hydroximinoyl chloride (**162**) by addition of triethylamine in the presence of a dipolarophile. At this concentration, the nitrile oxide has a half-life of approximately 3 days. Compared with the tertiary nitrile oxides (**22**) and (**104**), the nitrile oxide (**87**) was expected to exhibit lower reactivity towards 1,2-disubstituted alkenes as a result of its lower stability.



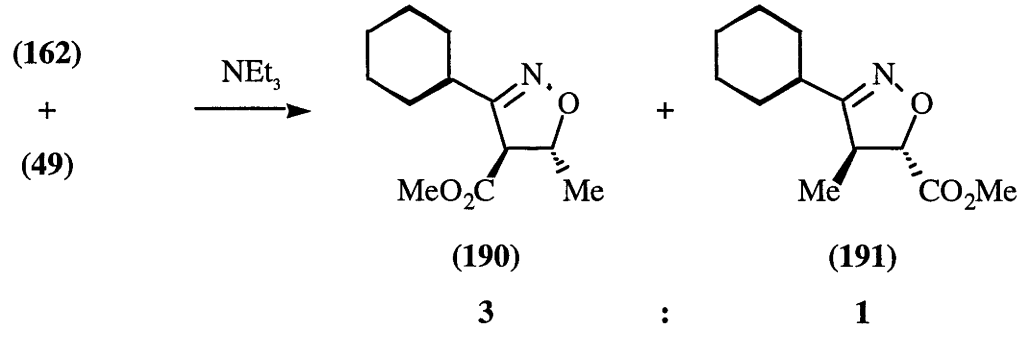
(189)

Scheme 69

Due to the instability of the hydroximinoyl chloride (**162**), the synthesis and elimination of this species was carried out in a one-pot procedure. In the presence of methyl acrylate (**34**), this procedure gave the isoxazoline (**189**) in a yield of 82% (Scheme 69). The adduct (**189**) was identified using its ^{1}H NMR spectrum. Characteristic isoxazoline resonances are visible at δ4.97 (triplet, 1H) and δ3.22 (doublet, 2H),

corresponding to the C5- and C4-protons, respectively, showing an AX_2 splitting pattern not unlike that of the methyldioxaneisoxazoline (**183**). The chemical shifts and integrations of the ^{1}H NMR signals are consistent with those of 5-methoxycarbonylisoxazolines presented in the literature.[78]

In order to determine the extent of cycloaddition of the nitrile oxide (**87**) to methyl acrylate (**34**) the hydroximinoyl chloride (**162**) was treated with triethylamine in the presence of the dipolarophile (**34**) and an internal standard, methyl benzoate. The extent of cycloaddition was calculated by comparison of the signal intensities of the isoxazoline resonances of the cycloadduct (**189**) with that of the methyl ester resonance of the internal standard in the ^{1}H NMR spectrum of this reaction mixture. This indicated a quantitative yield. The cycloaddition of the nitrile oxide (**87**) to methyl acrylate (**34**) (Scheme 69) proceeded rapidly, with no further change in the ^{1}H NMR spectrum after 2 hours. The cycloaddition of the nitrile oxide (**87**) to methyl acrylate (**34**) was considerably more rapid than its decomposition, which has a half-life of 3 days under these conditions. This allowed a high extent of cycloaddition.



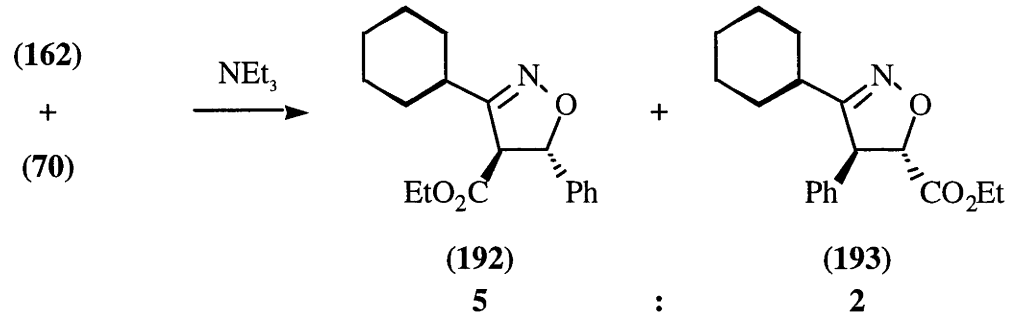
Scheme 70

In order to determine the extent of cycloaddition of cyclohexanecarbonitrile *N*-oxide (**87**) to the 1,2-disubstituted alkene methyl crotonate (**49**), the hydroximinoyl chloride (**162**) was treated with triethylamine in an NMR tube in the presence of the dipolarophile (**49**) and an internal standard, methyl benzoate (Scheme 70). The extent of cycloaddition was calculated by comparison of the signal intensities of the isoxazoline

resonances of the resultant cycloadducts (**190**) and (**191**) with that of the methyl ester resonance of the internal standard in the ^{1}H NMR spectrum of this reaction mixture. This indicated a yield of 70%. The cycloadducts (**190**) and (**191**) were not isolated but were identified by comparison of their ^{1}H NMR spectra with those of similar compounds in the literature.[78] The ^{1}H NMR spectrum of the major isomer (**190**) shows a pentet at δ4.82 and a doublet at δ3.61, which correspond to the C5- and C4-protons respectively. The ^{1}H NMR spectrum of the minor isomer (**191**) shows a doublet at δ4.48 and a multiplet at δ3.45, which correspond to the C5- and C4-protons respectively. This assignment is consistent with the analysis of the pair of stereoisomers resultant from the addition of the dithianenitrile oxide (**104**) to methyl crotonate (**49**) (Scheme 60, page 88), and similar examples in the literature.[78, 139] In addition, it is consistent with the small effect of the ethoxycarbonyl group in 5-ethoxycarbonylisoxazolines. The cycloaddition of the nitrile oxide (**87**) to methyl crotonate (**49**) was more rapid than its decomposition, which has a half-life of 3 days under these conditions. This allowed a high extent of cycloaddition.

The selectivity observed in favour of the 4-methoxycarbonylisoxazoline (**190**) in the cycloaddition of cyclohexanecarbonitrile *N*-oxide (**87**) to methyl crotonate (**49**) is lower than that seen with the methyldithianenitrile oxide (**104**), and intermediate between 2,2-dimethylpropanenitrile *N*-oxide (**18**) and benzonitrile oxide (**3**).[78] This indicates a steric influence, as the 3-dimensional steric requirements of the cyclohexane ring, a secondary sp^3 centre, are intermediate between the tertiary sp^3 centre of 2,2-dimethylpropanenitrile *N*-oxide (**18**) and the sp^2 centre of the benzene ring.

In order to determine the extent of cycloaddition of cyclohexanecarbonitrile *N*-oxide (**87**) to the 1,2-disubstituted alkene ethyl cinnamate (**70**), the hydroximinoyl chloride (**162**) was treated with triethylamine in an NMR tube in the presence of the dipolarophile (**70**) and an internal standard, methyl benzoate. The extent of cycloaddition was calculated by comparison of the signal intensities of the isoxazoline resonances of the resultant cycloadducts (**192**) and (**193**) with that of the methyl ester resonance of the



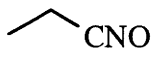
Scheme 71

internal standard in the ^{1}H NMR spectrum of this reaction mixture. This gave a combined yield of 71% of the isomers **(192)** and **(193)** in a ratio of 5:2 (Scheme 71). The cycloadducts **(192)** and **(193)** were not isolated but were identified by comparison of their ^{1}H NMR spectra with those of similar compounds in the literature.[78] The ^{1}H NMR spectrum of the major isomer **(192)** shows characteristic isoxazoline resonances at δ5.80 (1H, d) and at δ4.01 (1H, d) which correspond to the C5- and C4-protons, respectively. The ^{1}H NMR spectrum of the minor isomer **(193)** shows resonances at δ4.80 (1H, d) and at δ4.55 (1H, d), which correspond to the C5- and C4-protons, respectively. The cycloaddition of the nitrile oxide **(87)** to ethyl cinnamate **(70)** was more rapid than its decomposition, which has a half-life of 3 days under these conditions. This allowed a high extent of cycloaddition.

The ratio of 5-phenyl- to 4-phenyl-isoxazoline **(192)** to **(193)** in the cycloaddition of cyclohexanecarbonitrile *N*-oxide **(87)** to ethyl cinnamate **(70)** is 5:2, showing a lower preference for the 5-phenyl regioisomer **(192)** than is seen in the cycloaddition of adamantanecarbonitrile *N*-oxide **(22)** to the same dipolarophile, which gives a ratio of the 5-phenyl- to 4-phenyl-isoxazolines **(187)** and **(188)** of 3.8:1. This is consistent with the lower steric demand of the secondary nitrile oxide **(87)** compared to the tertiary nitrile oxide **(22)**, which results in less interaction between the dipole and the dipolarophile.

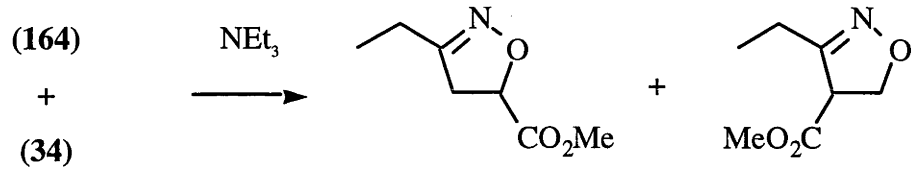
6.6 Propanenitrile N-*Oxide*

(164)



(17)

Propanenitrile *N*-oxide (**17**) is possessed of a low steric bulk and hence has a rapid rate of dimerisation compared to such other alkylnitrile oxides as cyclohexanecarbonitrile *N*-oxide (**87**) and adamantanecarbonitrile *N*-oxide (**22**). However, the half-life of dimerisation of the nitrile oxide (**87**), approximately 24 hours, is larger than the expected half-life of cycloaddition to alkenes, which should allow a good extent of cycloaddition.



(103) **(194)**

8 : **1**

Scheme 72

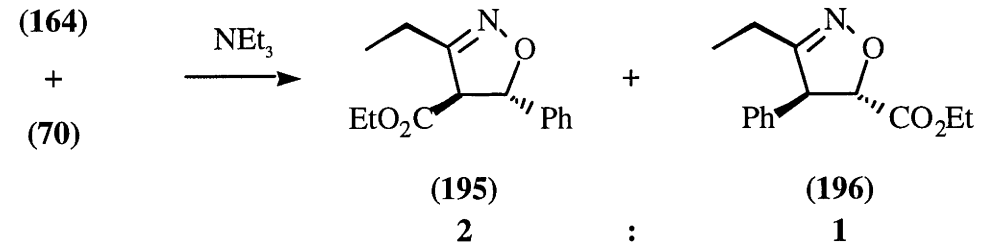
Due to the instability of the hydroximinoyl chloride (**164**), the synthesis and elimination of this species were carried out in a one-pot procedure in DMF. In the presence of methyl acrylate (**34**), this procedure gave a mixture of the isoxazolines (**103**) and (**194**) in a yield of 30% (Scheme 72). The ^{1}H NMR spectrum of the crude product mixture showed a ratio of the regioisomers (**103**) and (**194**) of 8:1. These isomers were separated and characterised by column chromatography, however the isolated yields of the isoxazolines (**103**) and (**194**) were 15% and 2% respectively, due to poor separation of these compounds on silica.

The ^{1}H NMR spectrum of the isoxazoline (**103**) shows resonances characteristic of a 5-methoxycarbonylisoxazoline at δ5.01 (1H, t, C5-H) and δ3.24 (2H, d, C4-H_2).[78] The isomeric isoxazoline (**194**) shows resonances characteristic of a 4-methoxycarbonylisoxazoline at δ4.63 (1H, apparent t), δ4.47 (1H, dd), and δ4.05 (1H,

dd).[78] The formation of the isomer **(194)** is consistent with the reduced steric constraints of the nitrile oxide **(17)**. According to the frontier orbital model of cycloadditions of Houk,[72] cycloadditions of nitrile oxides to monosubstituted dipolarophiles with electron withdrawing substituents show dipole LUMO-control with a small amount of HOMO-control as a result of the difference in orbital energies between the dipole and the dipolarophile. This results in the formation of 5-substituted isoxazolines as the major product, together with small amounts of 4-substituted isoxazolines.[70, 73] Usually, this effect is masked by steric effects, which favour 5-substituted isoxazolines through interaction of the nitrile oxide and the substituent on the isoxazoline. However, in the absence of strong steric interactions, as in the case of the primary alkylnitrile oxide **(17)**, the formation of 4-substituted isoxazolines can be observed.

The extent of cycloaddition of the nitrile oxide **(17)** to methyl acrylate **(34)** was determined by generating the nitrile oxide **(17)** in an NMR tube by elimination of the freshly prepared hydroximinoyl chloride **(164)** with triethylamine in the presence of the dipolarophile **(34)**. The extent of cycloaddition was calculated by comparison of the signal intensities of the isoxazoline resonances of the cycloadduct **(189)** with those of the methyl ester resonance of the internal standard, methyl benzoate in the ^{1}H NMR spectrum of the reaction mixture. The reaction took less than 1 hour before no further change was observed in the ^{1}H NMR spectrum. This indicates a yield of the isoxazoline **(103)** of 69%. The isoxazoline **(194)** was not observed in this experiment. The expected level of formation of this isoxazoline is below the detection limits of the ^{1}H NMR spectrometer.

The extent of cycloaddition of propanenitrile *N*-oxide **(17)** to the 1,2-disubstituted alkene ethyl cinnamate **(70)** was determined by generating the nitrile oxide **(17)** in an NMR tube by elimination of the freshly prepared hydroximinoyl chloride **(164)** with triethylamine in the presence of the dipolarophile **(70)** (Scheme 73). The extent of cycloaddition was calculated by comparison of the signal intensities of the isoxazoline resonances of the cycloadducts **(195)** and **(196)** with those of the methyl ester resonance of



(195) : (196)
2 : 1

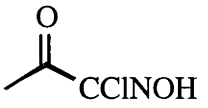
Scheme 73

the internal standard, methyl benzoate, in the ^{1}H NMR spectrum of the reaction mixture. No change in the ^{1}H NMR spectrum of this reaction mixture was observed after 48 hours. This gave a combined yield of 36% for the isomers **(195)** and **(196)** in a ratio of 2:1. The cycloadducts **(195)** and **(196)** were not isolated but were identified by comparison of their ^{1}H NMR spectra with those of similar compounds in the literature.[78] The ^{1}H NMR spectrum of the major isomer **(195)** shows characteristic isoxazoline resonances at δ5.86 (1H, d) and at δ3.99 (1H, d) which correspond to the C5- and C4-protons respectively. The ^{1}H NMR spectrum of the minor isomer **(196)** shows resonances at δ4.85 (1H, d) and at δ4.51 (1H, d), which correspond to the C5- and C4-protons respectively.

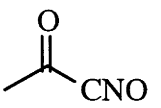
As in the case of the dioxanenitrile oxide **(160)**, the relatively high yields of cycloaddition of the nitrile oxide **(17)** can be rationalised as a difference in the rate of cycloaddition from the rate of decomposition. In this case the rate of dimerisation of propanenitrile *N*-oxide **(17)** is likely to be lower than the rate of cycloaddition of this nitrile oxide to ethyl cinnamate **(70)**, resulting in a reasonable yield of cycloadduct.

The difference in extent of cycloaddition of the nitrile oxides **(17)** and **(104)** is slight. This indicates that the nitrile oxide **(17)** is sufficiently stable at this concentration to undergo cycloaddition. The use of the nitrile oxide **(104)** as a masked form of the nitrile oxide **(17)** appears unlikely to offer a significant advantage in the synthesis of 3-ethylisoxazolines.

6.7 2-Oxopropanenitrile N-*Oxide*

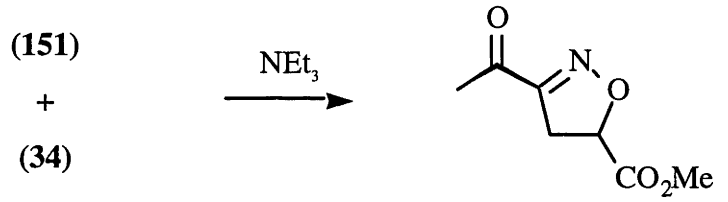


(151)



(61)

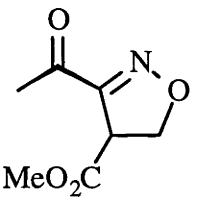
2-Oxopropanenitrile *N*-oxide **(61)** has a half-life in 0.05 M solution of less than 1 minute at room temperature, compared to 24 hours of the similarly-sized propanenitrile *N*-oxide **(17)**. The extremely rapid dimerisation of this nitrile oxide **(61)** was expected to result in a poor extent of cycloaddition to dipolarophiles.



(151) + **(34)**

(197)

Scheme 74



(198)

To examine this hypothesis the nitrile oxide **(61)** was generated by addition of triethylamine to the hydroximinoyl chloride **(151)** in the presence of methyl acrylate **(34)** (Scheme 74). This gave the major product **(197)** in an isolated yield of 31%. The cycloadduct was identified using its ^{1}H NMR spectrum. The ^{1}H NMR spectrum of the isoxazoline **(197)** shows resonances characteristic of a 5-methoxycarbonylisoxazoline at δ5.20 (1H, t, C5-H) and δ3.42 (2H, d, C4-H_2), once more showing a simple AX_2 system. The chemical shifts are consistent with those methyl acrylate-derived isoxazolines described above and in the literature.[78, 138] The mass spectrum shows peaks above the

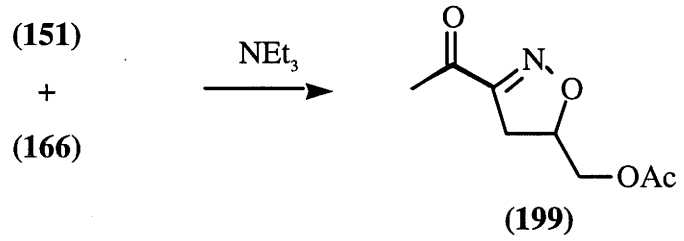
expected molecular ion; however, molecular analysis shows that the composition of the compound (**197**) is as expected for this structure. A trace of a second compound was also detected in the ^{1}H NMR spectrum of the crude reaction product. This product shows resonances at δ5.20 (1H, dd, C4-H), δ3.55 - 3.65 (1H, ABX multiplet, C5-H_2). The intensities of the signals show that this compound is not the isoxazoline (**198**); the chemical shifts are inconsistent with a 4-methoxycarbonylisoxazoline, which would give two doublets of doublets (1H each) with chemical shifts of around δ4.5 - 4.8 for the 5-protons and an ABX multiplet at around δ4.5 (1H) for the 4-proton.[78] This compound was not purified due to the poor yield.

In order to determine the extent of cycloaddition of the nitrile oxide (**61**) to methyl acrylate (**34**) the hydroximinoyl chloride (**151**) was treated with triethylamine in an NMR tube in the presence of the dipolarophile (**34**) and an internal standard, methyl benzoate. The extent of cycloaddition was calculated by comparison of the signal intensities of the isoxazoline resonances of the cycloadduct (**197**) with that of the methyl ester resonance of the internal standard in the ^{1}H NMR spectrum of this reaction mixture. The extent of reaction of the nitrile oxide (**61**) to methyl acrylate (**34**) was found to be 29%. The minor product was not visible in the ^{1}H NMR cycloaddition experiment. The expected yield of this product, relative to the amount of the major isomer (**197**) formed, was below the limits of detection by ^{1}H NMR spectroscopy in this experiment.

This extent of reaction is considerably lower than that shown by any other nitrile oxide in this study. This is likely to be a direct result of its instability; the half-life of dimerisation at < 5 minutes in an 0.05 M solution is faster than the expected half-life of cycloaddition at approximately 30 minutes.

Treatment of the hydroximinoyl chloride (**151**) with triethylamine in the presence of allyl acetate (**166**) gave the isoxazoline (**199**), which was purified by column chromatography with a final yield of 14% (Scheme 75). The isoxazoline (**199**) was identified using its ^{1}H NMR spectrum. The ^{1}H NMR spectrum of the isoxazoline (**199**)

shows a multiplet at δ5.01 (1H, C5-H), and two sets of doublets of doublets at δ3.22 and δ2.96 (1H each, C4-H_2), consistent with the isoxazoline **(155)** described above. No byproduct of the type seen in the reaction of the nitrile oxide **(61)** with methyl acrylate **(34)** was observed in the reaction with allyl acetate **(166)**. The compound **(199)** was unstable, decomposing on storage to a brown oil. No other product was observed in this reaction.



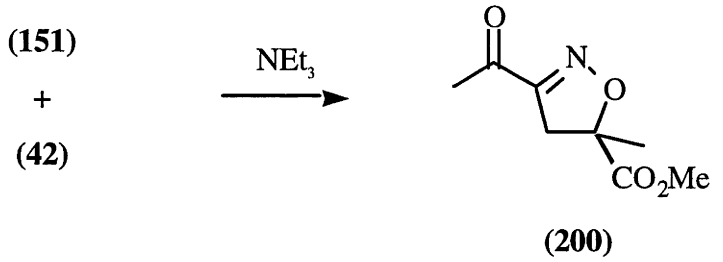
(199)

Scheme 75

In order to determine the extent of cycloaddition of the nitrile oxide **(61)** to allyl acetate **(166)**, the hydroximinoyl chloride **(151)** was treated with triethylamine in an NMR tube in the presence of the dipolarophile **(166)** and an internal standard, methyl benzoate. The extent of cycloaddition was then calculated by comparison of the signal intensities of the isoxazoline resonances of the cycloadduct **(199)** with that of the methyl ester resonance of the internal standard in the ^{1}H NMR spectrum of the reaction mixture. The extent of reaction of the nitrile oxide **(61)** to allyl acetate **(166)** was found to be 23%, which is similar to the extent of reaction with methyl acrylate **(34)**. Again, the poor extent of cycloaddition of the nitrile oxide **(61)** to allyl acetate **(166)** is likely to be related to the poor stability of the nitrile oxide **(61)**.

Treatment of the hydroximinoyl chloride **(151)** with triethylamine in the presence of methyl methacrylate**(42)** gave the isoxazoline **(200)**, which was purified by column chromatography in a yield of 11% (Scheme 76). The cycloadduct **(200)** was identified using its ^{1}H NMR spectrum. The ^{1}H NMR spectrum of the isoxazoline **(200)** shows two geminal coupled doublets at δ3.61 and δ3.02 (1H each, C4-H). These shifts are consistent with the C4-proton shifts of the isoxazolines **(197)**, **(199)** and **(168)**, and with those of

methyl 5-methyl-3-phenyl-isoxazoline-5-carboxylate (**44**).[136] The mass spectrum of the isoxazoline (**200**) shows a peak above the expected molecular ion; however, molecular analysis shows that the composition of the compound (**200**) is as expected for this structure. No byproduct of the type seen in the reaction of the nitrile oxide (**61**) with methyl acrylate (**34**) was observed in the reaction with methyl methacrylate(**42**).



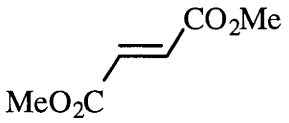
(200)

Scheme 76

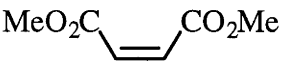
The extent of cycloaddition of the nitrile oxide (**61**) to methyl methacrylate (**42**) was determined by treatment of the hydroximinoyl chloride (**151**) with triethylamine in an NMR tube in the presence of the dipolarophile (**42**) and an internal standard, methyl benzoate. The extent of cycloaddition was calculated by comparison of the signal intensities of the isoxazoline resonances of the cycloadduct (**200**) with that of the methyl ester resonance of the internal standard in the ^{1}H NMR spectrum of the reaction mixture. The extent of reaction of the nitrile oxide (**61**) to methyl methacrylate (**42**) was found to be 27%, which is similar to the extent of reaction with methyl acrylate (**34**), indicating that the rate of cycloaddition of the nitrile oxide (**61**) to the 1,1-disubstituted dipolarophile (**42**) is similar to that to the monosubstituted alkene (**34**).

No evidence of cycloaddition was observed when the hydroximinoyl chloride (**151**) was treated with triethylamine in the presence of the 1,2-disubstituted alkenes dimethyl fumarate (**169**), dimethyl maleate (**171**), ethyl cinnamate (**70**) or methyl crotonate (**49**). This appears to be a direct result of the short lifetime of this nitrile oxide (**61**). While the rate of cycloaddition to monosubstituted alkenes remains rapid enough to show some extent of reaction, the rate of reaction to disubstituted alkenes is somewhat slower.

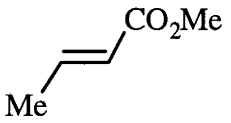
Therefore, the nitrile oxide (**61**) dimerises in preference to cycloadditions to disubstituted alkenes at the concentration studied.



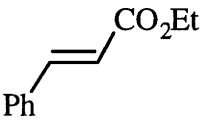
(**169**)



(**171**)



(**49**)



(**70**)

2-Oxopropanenitrile *N*-oxide (**61**) shows a marked difference in reactivity towards dipolarophiles compared to 2-methyl-1,3-dithiane-2-carbonitrile *N*-oxide (**104**). At a similar concentration, the nitrile oxide (**61**) shows a much lower extent of reaction with mono- and 1,1-disubstituted alkenes than the larger analogue (**104**). The nitrile oxide (**61**) shows no reaction at all with the more sterically demanding 1,2-disubstituted alkenes (**169**), (**171**), (**49**) and (**70**), in contrast to the high yields seen with the dithianenitrile oxide (**104**). This appears to be a direct result of the short lifetime of the nitrile oxide (**61**): decomposition occurs more rapidly than cycloaddition. As a result of this, the use of the nitrile oxide (**104**) as a masked form of the nitrile oxide (**61**) offers significant advantages in terms of extent of reaction towards dipolarophiles.

6.8 Summary

It is clear from the results presented above that the lifetime of a nitrile oxide in solution has an effect on the extent of cycloaddition to dipolarophiles. The short-lived nitrile oxides, 2-methyl-1,3-dioxane-2-carbonitrile *N*-oxide (**160**) and 2-oxopropanenitrile oxide (**61**), show limited reactivity towards dipolarophiles under the conditions used. More stable nitrile oxides, 2-methyl-1,3-dithiane-2-carbonitrile *N*-oxide (**104**), 2-butyl-

1,3-dithiane-2-carbonitrile *N*-oxide (**106**) and cyclohexanecarbonitrile *N*-oxide (**87**), show a relatively high extent of cycloaddition.

The difference in extent of reaction between the primary alkylnitrile oxide propanenitrile *N*-oxide (**17**) and the tertiary nitrile oxides methyldithianenitrile oxide (**104**) and adamantanecarbonitrile *N*-oxide (**22**) to ethyl cinnamate (**70**) is slight. Primary nitrile oxides are generally considered to be unreactive in cycloadditions due to their short lifetime.[4, 45, 46] The primary alkyl nitrile oxide (**17**), however, shows a reasonable extent of cycloaddition to dipolarophiles, as expected from its surprisingly high stability based on this current work. The propensity of primary alkylnitrile *N*-oxides towards cycloaddition seems comparable to that of tertiary alkylnitrile oxides, greater stability notwithstanding.

The difference in extent of reaction between 2-oxopropanenitrile *N*-oxide (**61**) and the other nitrile oxides in this study is striking. Of all the nitrile oxides studied, only the nitrile oxide (**61**) completely fails to undergo cycloaddition with 1,2-disubstituted alkenes.

The methyldithianenitrile oxide (**104**) can be considered a masked form of both of the nitrile oxides (**17**) and (**61**). However, considering the relatively high extent of cycloaddition of propanenitrile *N*-oxide (**17**), and the poor extent of reaction of the 2-oxopropanenitrile *N*-oxide (**61**), compared to the extent of reaction of the methyldithianenitrile oxide (**104**), the nitrile oxide (**104**) is more likely to be of use as an analogue for 2-oxopropanenitrile *N*-oxide (**61**). Cycloadditions of this nitrile oxide (**104**) should therefore lead to the synthesis of 3-acylisoxazolines that are unavailable directly *via* the nitrile oxide (**61**).

Chapter 7: Removal of Steric Auxiliaries

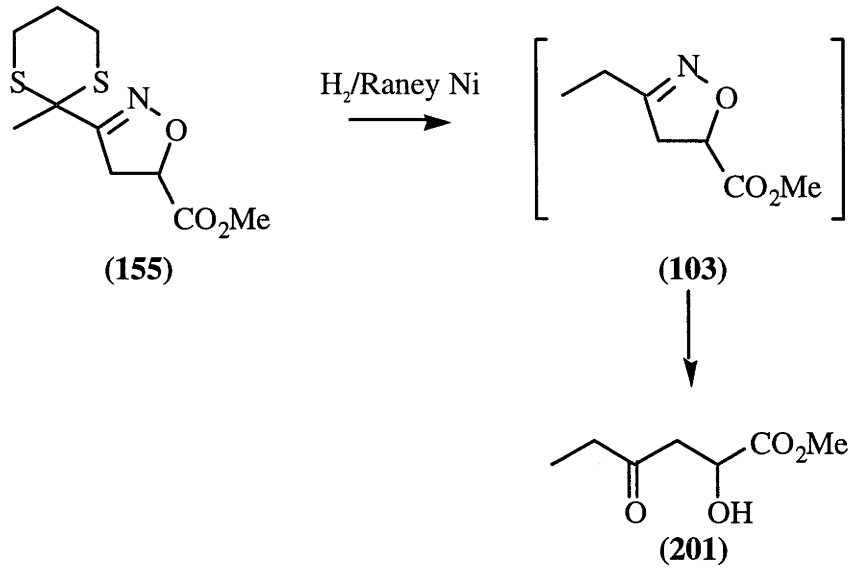
The nitrile oxide (**104**) acts as a masked form of the nitrile oxides (**61**) and (**17**). In order to investigate the use of the nitrile oxides (**104**) and (**106**) as analogues of alkyl- and acyl-nitrile oxides, it was necessary to consider the deprotection of the adducts of these nitrile oxides.

The nitrile oxide (**104**) allows the synthesis of 4,5-disubstituted 3-(2-methyl-1,3-dithian-2-yl)isoxazolines, which are masked forms of 3-acylisoxazolines. 4,5-Disubstituted-3-(2-methyl-1,3-dithian-2-yl)isoxazolines are readily synthesised using the nitrile oxide (**104**), while the analogous 4,5-disubstituted-3-acylisoxazolines are not available from the cycloadditions of the nitrile oxide (**61**). It was envisaged that the use of the dithiane subunit as a steric auxiliary would thus allow the synthesis of compounds otherwise unavailable by nitrile oxide cycloaddition chemistry due to the rapid decomposition of the nitrile oxides.

7.1 Reduction

Reduction using Raney nickel is a standard method of removing thioacetal protecting groups.[98] Raney nickel has also been shown to cause ring-opening in isoxazolines.[9, 101] It was envisaged that the cycloadducts of dithianenitrile oxide (**104**) with a range of dipolarophiles could be treated with Raney nickel in order to effect a combined ring-opening and deprotection procedure as illustrated in Scheme 77.

Treatment of the isoxazoline (**155**) with hydrogen gas in the presence of Raney nickel gave a mixture of unreacted starting material and the deprotected, ring opened product (**201**), in a ratio of approximately 1:1. The compound (**201**) was not isolated from this mixture but was identified by comparison of the ^{1}H NMR data with those presented in the literature.[140] The product (**201**) was identified using its ^{1}H NMR spectrum. The ^{1}H NMR spectrum shows signals at δ4.48 (t, 1H) and δ2.94 (ABX multiplet, 2H),

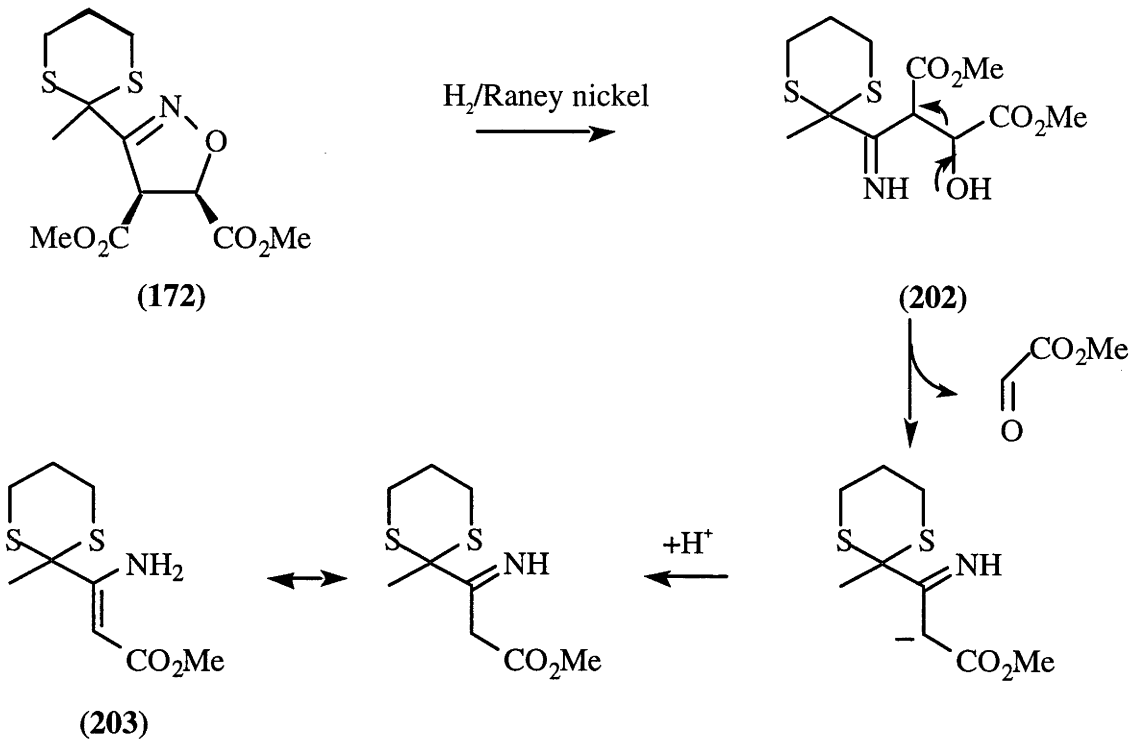


(155) **(103)** **(201)**

Scheme 77

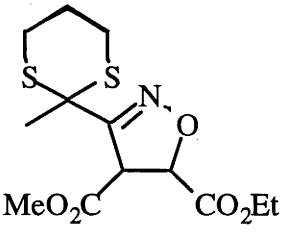
corresponding to the C2- and C3-protons respectively. Also present are signals representing the C5- and C6-protons at δ2.48 (q, 2H) and δ1.07 (t, 3H) respectively.

The treatment of the isoxazoline **(172)** with Raney nickel in ethanol gave a complex mixture of products. From this mixture was isolated starting material, the isoxazoline **(204)**, and compound **(203)**. The compound **(203)** was identified using mass and ^{1}H NMR spectroscopy. The mass spectrum shows a molecular ion at *m/z* 233, and the ^{1}H NMR spectrum shows a singlet at δ5.57 (1H), corresponding to an alkene proton. The isoxazoline **(204)** shows a ^{1}H NMR spectrum similar to that of the isoxazoline **(172)**. However, in place of the two methyl ester signals at δ3.75 and δ3.70 in the spectrum of the compound **(172)**, only one methyl ester signal is visible in the spectrum of the compound **(204)**, at δ3.70. The spectrum of the compound **(204)** also shows resonances at 4.20 (quartet, 2H) and δ1.25 (triplet, 3H) which are characteristic of an ethyl ester. The assignment of the isoxazoline **(204)** as the 5-ethoxycarbonyl structure rather than the 4-ethoxycarbonyl structure is arbitrary.



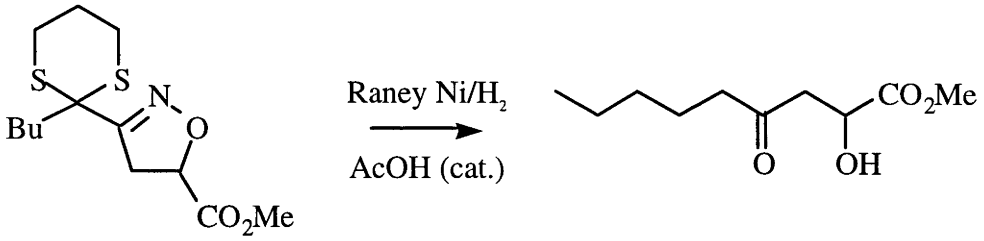
(172) **(202)** **(203)**

Scheme 78



(204)

It is likely that the β-amino-α,β-unsaturated ester **(203)** forms *via* the ring-opened product **(202)**. The compound **(202)** is then thought to decompose *via* a retroaldol reaction, eliminating methyl glyoxalate to give the compound **(203)**, as depicted in Scheme 78. This side reaction has been observed in isoxazolines where the resultant anion is stabilised by an electron withdrawing group.[101, 141] The product **(204)** is believed to result from transesterification of the isoxazoline **(172)** with the solvent, ethanol. The 1,3-dithiane subunit was present in each of the isolated products.



(179) **(205)**

Scheme 79

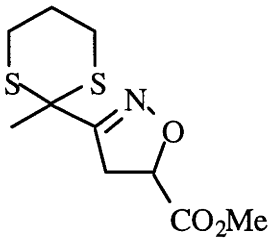
The reduction of the 3-(2-butyl-1,3-dithian-2-yl)isoxazoline **(179)** was carried out using hydrogen in the presence of acetic acid and Raney nickel according to the procedure of Curran[101] (Scheme 79). The reduction provided the reduced, ring-opened product **(205)** in 38% yield. Neither starting material nor any byproduct was isolated or observed by ^{1}H NMR spectroscopy. The reaction product was identified using its ^{1}H NMR and mass spectra. The ^{1}H NMR spectrum contained resonances at δ4.49 (dd, 1H) and δ2.93 (ABX multiplet, 2H), corresponding to the C2- and C3-protons respectively. Also present is a triplet signal at δ2.44 (2H) corresponding to the C5-proton.

Raney nickel reduction of the methyl 3-(2-alkyl-1,3-dithian-2-yl)isoxazoline-5-carboxylates **(155)** and **(179)** affords the desired 2-hydroxy-4-oxoalkanoates **(201)** and **(205)**. However, these reactions are quite inefficient. As the isoxazoline **(103)**, which is a precursor to methyl 2-hydroxy-4-oxohexanoate **(201)**, is readily available from the reaction of propanenitrile *N*-oxide **(17)** and methyl acrylate **(34)**, the use of the dithianenitrile oxides represents an unnecessarily complicated route to these compounds.

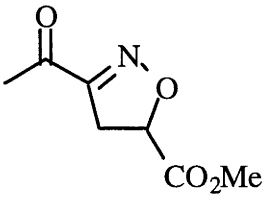
7.2 Hydrolysis

A number of procedures are available for the hydrolysis of dithianes in order to allow the synthesis of 3-acylisoxazolines. Due to the presence of ester groups on the isoxazolines, however, it was considered that oxidative hydrolysis would be preferable to

acid-catalysed hydrolysis. Oxidative hydrolysis would allow the removal of the dithiane moiety without affecting the ester functionality.



(155)

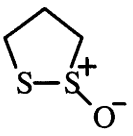


(197)

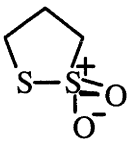
Initially, the isoxazoline **(155)** was treated with ceric(IV) ammonium nitrate in acetonitrile and water for 3 minutes according to the procedure of Ho *et al.*[93] The ^{1}H NMR spectrum of the product mixture showed a complex mixture of products. Signals corresponding to the expected reaction product, the isoxazoline **(197)**, were visible at δ5.20 (t, C5-H) and δ2.52 (s, CH_3C=O). However, these resonances were of relatively small intensity compared with those of the rest of the product mixture. The starting material **(155)** was not visible in the product mixture by either thin layer chromatography or ^{1}H NMR spectroscopy. A longer reaction time resulted in a slight increase in the amount of the hydrolysed isoxazoline **(197)** visible. This suggests that the unusual signals visible in the ^{1}H NMR spectrum may be an intermediate in the hydrolysis of the dithiane isoxazoline **(155)**. Of particular interest is a multiplet at δ5.0 - 5.1. This signal is in the same general region as many isoxazoline C5-protons. However, the multiplicity is much greater than expected for a single isoxazoline species. Due to the range of products observed in this reaction, other hydrolysis procedures were investigated.

The isoxazoline **(155)** was treated with silver nitrate, in the presence of iodine, according to the procedure of Nishide *et al.*[142] The ^{1}H NMR spectrum of the crude product mixture showed no hydrolysed product; only starting material was visible. As this hydrolysis was unsuccessful, the use of a different method of hydrolysis was investigated.

The isoxazoline (**155**) was treated with iron(III) nitrate nonahydrate according to the procedure of Hirano *et. al.*[95] The procedure gave the isoxazoline (**197**) in an isolated yield of 77%. The product isoxazoline (**197**) was identified by comparison of characteristic signals in its ^{1}H NMR spectrum with those of an authentic sample. A triplet signal at δ5.20 (1H, C5-H) and a doublet signal at δ3.42 (2H, C4-H_2) are indicative of this product, as is a singlet signal at δ2.52 (3H, 3-acetyl). The only other product observed in the NMR spectra of the crude product mixture was a compound showing ^{1}H NMR signals at δ3.75 (t, 1H), δ3.43 (t, 1H) and δ2.62 (p, 1H) and ^{13}C NMR signals at δ63.06, δ37.92 and δ29.55. From the multiplicity and splitting patterns of this species, it is likely that this product is derived from the dithiane ring. This compound was not purified. This



(206)

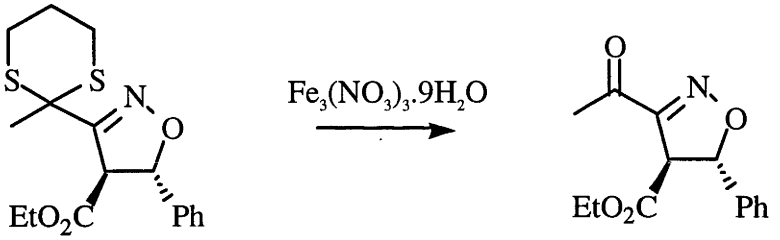


(207)

compound was believed to correspond to structure (**206**). Glass *et al.*[143] give the ^{1}H NMR data for the compound (**206**) as δ3.72 - 3.80 (1H, m), δ3.60 - 3.66 (1H, m), δ3.25 - 3.38 (1H, m) and δ2.85 - 3.00 (3H, m), which is significantly different from the spectrum observed in this case. However, the literature gives the ^{13}C NMR data for this compound as δ63.5, δ38.2 and δ29.9, corresponding closely to the observed signals in the crude product mixture.[143, 144] The ^{1}H NMR spectrum corresponds closely to that of the 1,3-dithiolane-1,1-dioxide (**207**) according to data given in the literature[143, 145] (δ3.70 (2H, t), δ3.40 (2H, t) and δ2.58 (2H, p)). However, the ^{13}C NMR data of the observed compound is different from that of the dithiolanedioxide (**207**) in the literature (δ58.2, δ36.7 and δ24.9). Due to the discrepancies between the observed chemical shifts and the literature, it is not clear whether the byproduct is either 1,3-dithiolane-1-oxide (**206**) or 1,3-dithiolane-1,1-dioxide (**207**). The byproduct was easily removed by chromatography. The use of a larger excess of iron(III) nitrate was expected to reduce the amount of this product in the filtrate by the

formation of a complex, allowing the byproduct to adhere to silica and hence be filtered out of solution. However, repeating the procedure with a larger excess of iron(III) nitrate did not result in a reduction of the amount of byproduct present.

The yield of the isoxazoline (**155**) from the oxime (**113**) was 55%; the yield of the isoxazoline (**197**) from the oxime was therefore 42%. This is comparable with the yield of the isoxazoline (**197**) from the hydroximinoyl chloride (**151**) of 31%, indicating that the synthesis of the isoxazoline (**197**) from the oxime (**113**) *via* the nitrile oxide (**104**) is a viable alternative to the synthesis from the hydroximinoyl chloride (**151**).

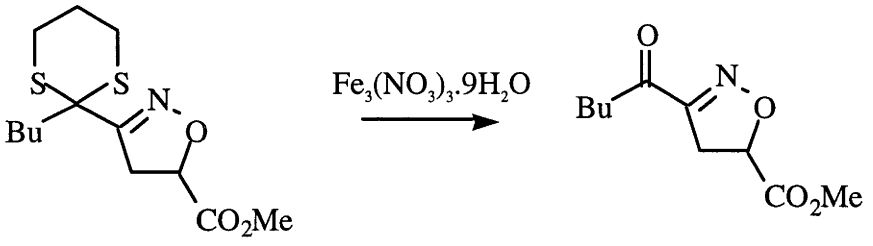


(**175**) (**208**)

Scheme 80

The oxidative hydrolysis of the 4,5-disubstituted isoxazoline (**175**) gave the 3-acetylisoxazoline (**208**) in an isolated yield of 84% (Scheme 80). The ^{1}H NMR spectrum of the crude product mixture showed resonances corresponding to the same reaction byproduct seen in the hydrolysis of the isoxazoline (**155**). The isoxazoline (**208**) was identified using its ^{1}H NMR spectrum. This spectrum shows a resonance at δ5.88 (doublet, 1H) which was assigned as the C5-proton signal due to its high shift, resulting from the combined deshielding effects of the phenyl moiety and the 1-oxygen. The C4-proton resonance is coincident with the resonance from the methylene protons of the ethyl ester, resulting in a multiplet of 3H intensity in the region δ4.2 to δ4.3. These chemical shifts are consistent with those of the isoxazoline signals of the parent compound (**175**). In addition, a singlet at δ2.57 (3H) represents 3-acetyl protons. Other spectral and physical data were consistent with the structure of the isoxazoline (**208**).

The isoxazoline (**208**) could not be synthesised from the reaction of the hydroximinoyl chloride (**151**) with ethyl cinnamate (**70**). This method therefore allows the synthesis of a 3-acylisoxazoline that is substituted in both the 4- and the 5-positions, which is unavailable *via* direct cycloaddition chemistry.

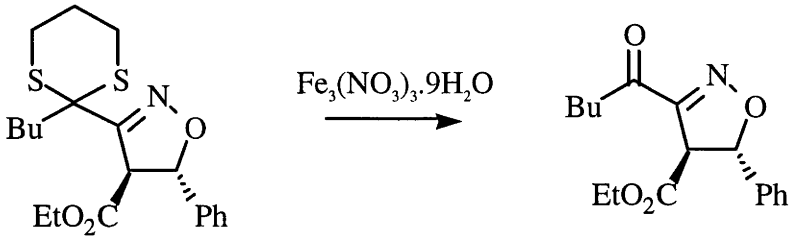


(**179**) (**209**)

Scheme 81

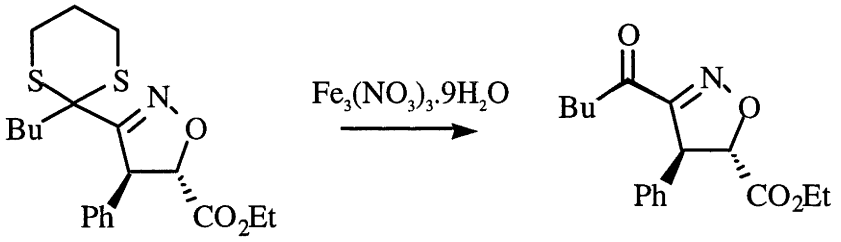
The hydrolysis of the isoxazoline (**179**) was carried out in an analogous manner to that described for the isoxazolines (**155**) and (**175**). The procedure resulted in the formation of methyl 3-pentanoyl-4,5-isoxazoline-5-carboxylate (**209**) in an isolated yield of 74% (Scheme 81). The ^{1}H NMR spectrum of the crude product mixture showed resonances corresponding to the same reaction byproduct seen in the hydrolysis of the isoxazoline (**155**). The product (**209**) was identified using its ^{1}H NMR spectrum. Signals at δ5.18 (t, 1H) and δ3.42 (d, 2H) represent the C5- and C4-protons respectively, while a signal at δ2.91 (t, 2H) represents the α-carbonyl protons on the C3-pentanoyl group.

The 3-(2-butyl-1,3-dithianyl)-isoxazolines (**180**) and (**181**) were each treated with iron(III) nitrate nonahydrate. The 5-phenylisoxazoline (**180**) gave the pentanoylisoxazoline (**210**) in an isolated yield of 48% (Scheme 82), while the isomeric 4-phenylisoxazoline (**181**) gave the pentanoylisoxazoline (**211**) in an isolated yield of 53% (Scheme 83). The ^{1}H NMR spectrum of each crude product mixture showed



(180) **(210)**

Scheme 82



(181) **(211)**

Scheme 83

resonances corresponding to the same reaction byproduct seen in the hydrolysis of the isoxazoline (**155**).

The comparatively poor yields for the hydrolysis of the compounds (**180**) and (**181**) are due to the poor separation of these isoxazolines from the reaction byproduct. Nevertheless, the protocol allows for the synthesis of a range of 4,5-disubstituted 3-acylisoxazolines.

7.3 Summary

The deprotection of the dithiane group by reduction or hydrolysis allows nitrile oxides of the type (**76**) to be used as analogues for the nitrile oxides (**17**) and (**61**). While the change in reactivity of the dithiane nitrile oxides (**104**) and (**106**) compared to the nitrile oxide (**17**) is relatively slight in practice, there is potential for the use of the lithiation protocol to allow access to a wide range of 3-alkylisoxazoline derivatives. This

could be done by variation of the electrophile used to quench the 2-lithio-1,3-dithiane anion in the synthesis of precursors to the nitrile oxides **(104)** and **(106)**.

Comparison of the cycloadditions of the nitrile oxides **(104)** and **(106)** with 2-oxopropanenitrile oxide **(61)** shows that the nitrile oxides **(104)** and **(106)** give a larger extent of reaction as a result of their longer lifetimes. As a result of this, the nitrile oxide **(104)** can be used to synthesise isoxazolines that are substituted in both the 4- and 5-positions, whose analogues are not available using the nitrile oxide **(61)**. The relatively simple deprotection procedure allows a high yield synthesis of 3-acetylisoxazolines from the parent 3-(2-methyl-1,3-dithianyl)-isoxazolines. In addition, since longer chain analogues of pyruvaldehyde oxime are not readily available, and the derived nitrile oxides are likely to be short-lived, the use of the longer-chain nitrile oxides such as the butyldithianenitrile oxide **(106)** provides potential access to a wide range of 4,5-substituted 3-acylisoxazolines.

Chapter 8: Conclusion

The work described in this thesis demonstrates the utility of steric auxiliaries in nitrile oxide cycloadditions. Initially considered were the cycloreversion of furoxans and the synthesis of a nitrile oxide on a solid support. Cycloreversion was shown to be ineffective in improving the yield of cycloadditions due to the high temperatures required, which resulted in the formation of a number of byproducts. The solid support procedure was not carried out due to the failure of the model compounds to react under the necessary conditions.

The synthesis and stability of a number of nitrile oxides were examined. In most cases, it was found that an increased steric bulk led to a greater stability. In order to exploit this effect, 2-methyl-1,3-dithiane-2-carbonitrile *N*-oxide was synthesised using 1,3-dithiane lithiation chemistry. This route was chosen due to the potential for synthesis of a range of analogues by varying the electrophile used to quench the 1,3-dithiane anion. This was demonstrated by the synthesis of a precursor to 2-butyl-1,3-dithiane carbonitrile *N*-oxide.

Propanenitrile *N*-oxide was found to be somewhat more stable than expected on the basis of the literature precedents. 2-Oxopropanenitrile *N*-oxide, however, was found to extremely unstable, and undergoes limited cycloaddition with monosubstituted alkenes and no cycloaddition with 1,2-disubstituted alkenes.

A correlation was observed between the rate of decomposition of a nitrile oxide and its extent of cycloaddition. Short-lived nitrile oxides showed poor or no cycloaddition towards 1,2-disubstituted alkenes, while longer-lived nitrile oxides showed mid to high levels of cycloaddition to 1,2-disubstituted alkenes.

The utility of the 1,3-dithiane as a steric auxiliary was investigated. The increased steric bulk of the 1,3-dithianenitrile oxides allowed a greater extent of cycloaddition than

that shown by 2-oxopropanenitrile *N*-oxide. The removal of this moiety was effected by reductive and hydrolytic methods. Reduction was found to be inefficient. However, the hydrolysis of cycloadducts of 1,3-dithianenitrile oxides led to 3-acylisoxazolines that are unavailable *via* the cycloaddition of acylnitrile oxides.

Experimental – General

Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected. Solvents were purified using standard procedures and all reactions were conducted under nitrogen unless otherwise stated. Ether refers to diethyl ether. THF refers to tetrahydrofuran. THF was distilled from potassium with benzophenone as an indicator. DMF refers to *N,N*-dimethylformamide. Starting materials were purchased from Sigma-Aldrich chemical company. TLC analyses of reaction mixtures were performed on aluminium backed plates of Kieselgel 60_{F254} silica and were visualised with 254 nm lamp or an ethanol solution of 5% phosphomolybdic acid. Column chromatography was carried out on Merck silica gel 60_{PF254}.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer in *d*-chloroform unless otherwise stated and were referenced to either tetramethylsilane or residual chloroform in the solvent. Chemical shifts are quoted as δ in parts per million downfield from tetramethylsilane. Multiplicities used to define signal shape for ^{1}H and ^{13}C NMR spectra are abbreviated to: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; sx, sextet; m, multiplet; br, broad. Signal assignments for isoxazolines refer to the isoxazoline ring unless otherwise noted. H_a and H_e denote axial and equatorial protons respectively. Infrared spectra were recorded on a Perkin Elmer 1800 FT IR spectrophotometer. All mass spectra are low resolution electron impact spectra unless otherwise stated. Electron impact and chemical ionisation spectra were recorded on a Fison Instruments VG Autospec mass spectrometer at 70 eV.

Microanalyses were performed by the Microanalytical Services Unit of the Research School of Chemistry, Australian National University.

Adamantane-1-carboxaldehyde oxime (**146**) and Adamantanyl-chloro(hydroxyimino)methane (**161**) were prepared by the method of Mariana Gebara.[141]

Experimental – Chapter 2

3,4-Bis(ethoxycarbonyl)furoxan (66)

A solution of diethyl nitromalonate (**88**) (2.05 g, 5 mmol) in decahydronaphthalene (5 ml) was heated at reflux for 16 h. The solvent was then removed *in vacuo*. The residue was dissolved in chloroform and filtered though neutral alumina. The filtrate was concentrated *in vacuo* and then purified by successive Kügelrohr distillations (120-130°C, 5 torr) to give the title compound as a colourless oil (58 mg, 0.25 mmol, 5%, lit:[146] 75%).

^{1}H NMR: δ4.50 (2H, q, J = 7.0 Hz, -C$\underline{H}_2$CH$_3$), 4.45 (2H, q, J = 7.0 Hz, -C$\underline{H}_2$CH$_3$), 1.45 (3H, t, J = 7.0 Hz, -CH$_2$C$\underline{H}_3$) 1.39 (3H, t, J = 7.0 Hz, -CH$_2$CH$_3$). ^{13}C NMR: δ156.65 (-CO$_2$-), 155.08 (-CO$_2$-), 148.33 (C=N), 63.61 (-$\underline{C}$H$_2$CH$_3$), 13.85 (-CH$_2\underline{C}$H$_3$).

^{1}H NMR (500 MHz, d_8-toluene): 3.95 (2H, q, J = 7.1 Hz, -C$\underline{H}_2$CH$_3$), 3.84 (2H, q, J = 7.1 Hz, -C$\underline{H}_2$CH$_3$), 0.94 (3H, t, J = 7.1 Hz, -CH$_2$C$\underline{H}_3$), 0.89 (3H, t, J = 7.1 Hz, -CH$_2$C$\underline{H}_3$).

Benzohydroximinoyl chloride (2)

Benzaldehyde (**89**) (5.0 g, 47 mmol) was dissolved in a mixture of ethanol (12 ml) and ice/water (30 ml). Hydroxylamine hydrochloride (3.7 g, 52 mmol) was dissolved in the mixture, followed by the dropwise addition of a 50% aqueous solution of sodium hydroxide (15 ml). The mixture was stirred for 1.5 h. The mixture was washed with ether (50 ml), separated, and the aqueous layer was acidified to pH 3 with concentrated hydrochloric acid. The aqueous layer was then extracted with ether (2 x 50 ml), and the combined organic layers were washed with water (3 x 50 ml) and filtered though phase-separation filter paper. The solvent was removed *in vacuo* to give a yellow oil which was used without further purification (4.61g, 38 mmol, 81%). To a solution of this oil (4.2 g, 35 mmol) in DMF (30 ml) was added *N*-chlorosuccinimide (4.7 g, 35 mmol). The

resultant exothermic reaction caused the temperature to exceed 50°C, despite an ice/salt bath. On cessation of exothermic reaction, the mixture was poured into an ice/water mixture (100 ml) and extracted with ether (2 x 50 ml). The combined organic layers were washed with water (3 x 50 ml), filtered though phase-separation filter paper and the solvent was removed *in vacuo* to give a pale yellow solid. The product was recrystallised from hexane to give the title compound as a colourless crystalline compound (1.5 g, 9.6 mmol, 23 % yield). A second crop of pale yellow crystals (1.2 g) was also collected, which were used without further purification.

mp: 47-50°C (lit:[18] 48°C). ^{1}H NMR: δ7.97 (1H, s, -CClNOH), 7.35-7.45 (5H, m, Ar H).

3,4-Diphenylfuroxan (68)

Benzohydroximinoyl chloride (**92**) (1.0 g, 6.4 mmol) was dissolved in THF (50 ml) and triethylamine (1.0 ml, 0.73 g, 7.1 mmol) was added. The solvent was removed *in vacuo* and the residue was taken up in chloroform (50 ml). This solution was washed with water (3 x 50 ml), filtered though phase-separation filter paper and the solvent was removed *in vacuo* to givea pale yellow oil. The residue was allowed to stand for 16 hours, after which time the resultant yellow solid was recrystallised from hexane to give the title compound as a pale yellow powder (0.69 g, 2.9 mmol, 91%).

mp. 114-117°C (lit:[48] 114-115°C). ^{1}H NMR: δ7.4-7.6 (m, Ar H). MS: *m/z* 238 (rel. intensity: 24) $[M]^+$, 178 (bp) $[M - N_2O_2]^+$, 152, 126, 119 $[Ph\text{-}CNO]^+$, 89, 77 $[Ph]^+$.

2,6-Dichlorobenzohydroximinoyl chloride (92)

To a solution of 2,6-dichlorobenzaldoxime (**91**) (2.5 g, 13 mmol) in DMF (13 ml) was added *N*-chlorosuccinimide (1.7 g, 13 mmol) in 5 portions over 30 min. The resultant exothermic reaction was kept below 40°C using an ice/salt bath. The reaction mixture was then poured into an ice/water mixture (50 ml) and extracted with ether (2 x 50 ml). The

combined organic fractions were washed with water (3 x 50 ml) and filtered though phase-separation filter paper, and the solvent was removed *in vacuo*. The product was recrystallised from hexane to give the title compound as a white solid (1.7 g, 7.7 mmol, 59%).

mp: 88-90°C (lit:[84] 91-92°C). ^{1}H NMR: δ8.31 (1H, s, -CClNOH), 7.30-7.45 (3H, m, Ar H).

3,4-Bis(2,6-dichlorobenzo)furoxan (69)

2,6-Dichlorobenzohydroximinoyl chloride (**92**) (0.21 g, 0.96 mmol) was dissolved in THF (10 ml). Triethylamine (0.19 ml, 14 mg, 1.4 mmol) was added and the reaction mixture was heated at reflux and stirred overnight. The reaction mixture was cooled and the solvent was removed *in vacuo*. The residue was taken up in chloroform (10 ml) and washed with water (2 x 10 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was allowed to stand for 6 weeks, after which time the resultant yellow solid was recrystallised from hexane to give the title compound as a yellow solid (0.16 g, 0.85 mmol, 89%).

mp: 192-195°C (lit:[48] 199-200°C). ^{1}H NMR: δ7.3-7.45 (m, Ar H). MS: *m/z* 376 (rel. intensity: 6) $[M]^+$, 316 (bp) $[M - N_2O_2]^+$, 244 $[M - N_2O_2 - C_3H_2Cl]^+$, 208, 188 $[2,6\text{-}Cl_2Ph\text{-}CNO]^+$, 187, 174, 157, 124.

Reaction of 3,4-diphenylfuroxan (68) with ethyl *trans*-cinnamate (70) in tetrahydrofuran

3,4-Diphenylfuroxan (**68**) (0.50 g, 2.1 mmol) was dissolved in THF (8 ml). Ethyl *trans*-cinnamate (**70**) (0.70 ml, 0.74 g, 4.2 mmol) was added and the mixture heated at reflux and stirred for 3 h. On cooling, the solvent was removed *in vacuo*. NMR spectroscopy showed only signals corresponding to starting materials.

Reaction of 3,4-bis(2,6-dichlorobenzo)furoxan (69) with ethyl *trans*-cinnamate (70) in tetrahydrofuran

3,4-bis(2,6-Dichlorobenzo)furoxan **(69)** (0.50 g, 1.3 mmol) was dissolved in THF (8 ml). Ethyl *trans*-cinnamate **(70)** (0.44 ml, 0.47 g, 2.6 mmol) was added and the mixture heated at reflux and stirred for 3 h. On cooling, the solvent was removed *in vacuo*. NMR spectroscopy showed only signals corresponding to starting materials.

Reaction of 3,4-diphenylfuroxan (68) with ethyl *trans*-cinnamate (70)

3,4-Diphenylfuroxan **(68)** (10 mg, 42 mmol) and ethyl *trans*-cinnamate **(70)** (7 ml, 7.4 mg, 42 mmol) were combined in 1,2,4-trimethylbenzene (5 ml). The reaction mixture was heated at reflux for 4 days. The solvent was removed *in vacuo* and the residue was transferred to an NMR tube with *d*-chloroform. *t*-Butyl methyl ether (7.2 mg) was added as a standard. No signals corresponding to a cycloaddition product were observed by ^{1}H NMR.

The procedure was repeated as above using 1,4,6-trichlorobenzene as a solvent. ^{1}H NMR signals corresponding to the chemical shifts reported in the literature[107, 108] for the isomer ethyl 3,5-diphenyl-4,5-dihydroisoxazole-4-carboxylate **(72a)** were observed at δ5.99 (1H, d, J = 6.5 Hz, C5-H) and 4.46 (1H, d, J = 6.5 Hz, C4-H).[107, 108] Using *t*-butyl methyl ether (9.3 mg) as a standard, the yield was calculated at approximately 15% by comparison of signal intensities.

Reaction of 3,4-bis(2,6-Dichlorobenzo)furoxan (69) with ethyl *trans*-cinnamate (70)

3,4-Bis(2,6-dichlorobenzo)furoxan **(69)** (10 mg, 27 mmol) and ethyl *trans*-cinnamate **(70)** (4.5 ml, 4.8 mg, 27 mmol) were combined in 1,2,4-trimethylbenzene (5 ml). The reaction mixture was heated at reflux for 4 days. The solvent was removed *in vacuo* and the residue was transferred to an NMR tube with *d*-chloroform. *t*-Butyl methyl ether (7.4 mg) was added as a standard. ^{1}H NMR signals corresponding to the chemical

shifts reported in the literature[84] for ethyl 3-(2,6-dichlorophenyl)-5-phenylisoxazole-4-carboxylate (**72b**) and ethyl 3-(2,6-dichlorophenyl)-4-phenylisoxazole-5-carboxylate (**73b**) were observed. Comparison of signal intensities with those of the standard gave a total yield of approx. 10-25%.

Ethyl 3-(2,6-dichlorophenyl)-5-phenylisoxazole-4-carboxylate (**72b**): ^{1}H NMR: δ6.24 (1H, d, J = 9 Hz, C5-H), 4.57 (1H, d, J = 9 Hz, C4-H).[84]

Ethyl 3-(2,6-dichlorophenyl)-4-phenylisoxazole-5-carboxylate (**73b**): ^{1}H NMR: δ5.28 (1H, d, J = 5.5 Hz, C5-H), δ5.25 (1H, d, J = 5.5 Hz, C4-H).[84]

The procedure was repeated as above using 1,4,6-trichlorobenzene as a solvent. Only the ethyl 3-(2,6-dichlorophenyl)-5-phenylisoxazole-4-carboxylate (**72b**) was observed. Using *t*-butyl methyl ether (6.5 mg) as a standard, the yield was calculated at approximately 10%.

Experimental – Chapter 3

<u>*N*-(*t*-Butoxycarbonyl)-β-nitroalanine *t*-butyl ester (94)</u>

N-(*t*-Butoxycarbonyl)glycine (0.75 g, 4.3 mmol), *N*,*N*-dicyclohexylcarbodiimide (0.97 g, 4.7 mmol), *t*-butyl alcohol (2.0g, 27 mmol) and 4-dimethylaminopyridine (0.10 g, 0.80 mmol) were combined in ether (100 ml). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then filtered, and the filtrate was washed with water (50 ml), 5% acetic acid solution (50 ml) and again with water (50 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo* to give a colourless oil. The oil was found to contain acetic acid, which was removed by taking the oil up in ether and removing the solvent under a stream of nitrogen. This was repeated until a negligible amount of acetic acid was observed by ^{1}H NMR spectroscopy. The final yield of the protected glycine derivative (**95**) was 0.62 g (2.7 mmol, 62%).

^{1}H NMR: δ5.0 (1H, br s, NH), 3.80 (2H, br d, CH_2), 1.47 (9H, s, -C(CH_3)$_3$, boc-group), 1.46 (9H, s, -C(CH_3)$_3$, ester). These ^{1}H NMR data are consistent with those reported in the literature.[147]

The glycine derivative (0.62 g, 2.7 mmol) was dissolved in carbon tetrachloride (150 ml). To this solution was added *N*-bromosuccinimide (0.47 g, 2.7 mmol). The solution was heated at reflux and irradiated for 15 min with a UV lamp. The mixture was filtered on cooling, and the solvent was removed *in vacuo* at room temperature to give a brown oil. The compound was refrigerated overnight and was used without further purification. A solution of nitromethane (0.33 g, 5.4 mmol) in THF (20 ml) was cooled to –84°C in an ethyl acetate/liquid nitrogen bath, and a 15% solution of *n*-butyllithium in hexane (2.3 ml, 0.35 g, 5.4 mmol) was added. The solution was stirred at –84°C for 30 min, then a solution of the brown oil in THF (20 ml) was added in a dropwise manner and the mixture was stirred for 7 h. The solvent was then removed *in vacuo* and the residue

was partitioned between ethyl acetate and water. The organic layer was separated, dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The resultant oil was purified by flash chromatography (17% ethyl acetate in hexane) to give the title compound as a white solid (95 mg, 0.34 mmol, 13% from *N*-boc-glycine *t*-butyl ester, lit:[109] 63%).

mp 97-98°C (lit:[109] 99-100°C). ^{1}H NMR: δ5.47 (1H, br d, J = 6.8 Hz, NH), 4.92 (1H, dd, J = 3.5, 15 Hz, β-CH), 4.78 (1H, dd, J = 3.5, 15 Hz, β-CH), 4.55-4.6 (1H, m, α-CH), 1.50 (9H, s, -C(CH_3)$_3$, boc-group), 1.47 (9H, s, -C(CH_3)$_3$, ester). These ^{1}H NMR data are consistent with those presented in the literature.[109]

Attempted cycloaddition reaction of *N*-(*t*-butoxycarbonyl)-β-nitroalanine *t*-butyl ester (94) to methyl acrylate (34)

To a solution of *N*-boc-β-nitroalanine *t*-butyl ester **(94)** (9.6 mg, 35 mmol) in toluene (5 ml) was added methyl acrylate **(34)** (6.3 ml, 6.0 mg, 70 mmol), phenyl isocyanate (7.6 ml, 8.4 mg, 70 mmol) and triethylamine (approx. 1 ml). The reaction mixture was heated at reflux and stirred for 16 h. On cooling, the solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the residue showed only signals corresponding to the starting materials, with no signals corresponding to a cycloadduct.

Attempted cycloaddition reaction of *N*-(*t*-butoxycarbonyl)-β-nitroalanine *t*-butyl Ester (94) to ethyl *trans*-cinnamate (70)

To a solution of *N*-boc-β-nitroalanine *t*-butyl ester **(94)** (10 mg, 37 mmol) in toluene (5 ml) was added ethyl *trans*-cinnamate **(70)** (13 ml, 14 mg, 77 mmol), phenyl isocyanate (8.3 ml, 9.1 mg, 77 mmol) and triethylamine (approx. 1 ml). The reaction mixture was heated at reflux and stirred for 20 h. On cooling, the solvent was removed *in vacuo*. The NMR spectrum of the residue showed only signals corresponding to the starting materials, with no signals corresponding to a cycloadduct.

Cycloaddition reaction of 1-nitropropane (102) to methyl acrylate (34)

To a solution of 1-nitropropane (**102**) (0.10 ml, 0.10 g, 1.1 mmol) in THF (10 ml) was added methyl acrylate (**34**) (0.20 ml, 0.19 g, 2.2 mmol), phenyl isocyanate (0.27 g, 0.24 ml, 2.2 mmol) and a drop of triethylamine. The reaction was stirred for 2 days, after which no precipitate was observed. The solvent was removed *in vacuo* to give a waxy colourless powder. This powder was suspended in dichloromethane and filtered, and the filtrate was concentrated *in vacuo*. The ^{1}H NMR spectrum of the residue contained signals corresponding to the presence of methyl 3-ethyl-4,5-dihydroisoxazole-5-carboxylate (**103**), and a small amount (approx 15%) of 1-nitropropane (**102**).

Methyl 3-ethyl-4,5-dihydroisoxazole-5-carboxylate (**103**): ^{1}H NMR: δ5.01 (1H, t, J = 9 Hz, C5-H), 3.81 (3H, s, -OCH_3), 3.24 (2H, d, J = 9 Hz, C4-H_2), 2.41 (2H, q, J = 7.5 Hz, C3-C$\underline{H}_2$$CH_3$), 1.20 (3H, t, J = 7.5 Hz, C3-CH_2C$\underline{H}_3$). ^{13}C NMR: δ170.92 (-$\underline{C}O_2CH_3$), 159.32 (C3), 76.73 (C5), 52.62 (-$CO_2\underline{C}H_3$), 40.72 (C4), 20.79 (C3-$\underline{C}H_2CH_3$), 10.66 (C3-$CH_2\underline{C}H_3$). MS: *m/z* 158 (rel. intensity 61) $[M + H]^+$, 140, 130, 112, 102, 98 $[M - CO_2CH_3]^+$, 70 (bp), 59 $[CO_2CH_3]^+$, 55. Anal. for $C_7H_{11}NO_3$ Calc: C: 53.49, H: 7.05, N: 8.91. Found: C: 53.44, H: 7.02, N: 9.14.

Attempted cycloaddition reaction of methyl 3-nitropropanoate (97) to ethyl *trans*-cinnamate (70)

To a solution of methyl 3-nitropropanoate (**97**) (10 mg, 75 mmol) in toluene (5 ml) was added phenyl isocyanate (16 μl, 18 mg, 0.15 mmol), ethyl *trans*-cinnamate (**70**) (25 μl, 26 mg, 0.15 mmol) and triethylamine (5 μl). The reaction mixture was heated at reflux and stirred for 2 days. On cooling, the solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the residue showed only signals corresponding to the starting materials, with no signals corresponding to a cycloadduct.

Reaction of methyl 4-nitrobutanoate (99) with phenyl isocyanate

To a solution of methyl 4-nitrobutanoate **(99)** (9.6 µl, 11 mg, 75 mmol) in dry THF (5 ml) was added triethylamine (2 µl) and phenyl isocyanate (16 µl, 18 mg, 0.15 mol). The reaction mixture was stirred for 4 h at room temperature and the solvent was removed *in vacuo*. ^{1}H NMR analysis of the crude reaction product showed only signals corresponding to the starting materials.

Experimental – Chapter 4

2-Methyl-1,3-dithiane (109) – from 1,3-dithiane

A solution of 1,3-dithiane **(77)** (4.0 g, 33 mmol) in dry THF (80 ml) was stirred at –60°C in a dry-ice/acetone bath. A 15% solution of *n*-butyllithium in hexane (26 ml, 3.8 g, 60 mmol) was added to this solution by syringe. The temperature was kept below –60°C during the addition. The reaction mixture was warmed to –30°C and stirred for 3 h at this temperature. Methyl iodide (12 ml, 29 g, 0.20 mol) was then added in a dropwise manner. The reaction mixture was then stirred at 4°C for 16 h. The reaction mixture was then poured into ice/water (approx. 100 ml). This mixture was extracted with ether (4 x 50 ml) and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*, to give the title compound as a pale yellow oil (1.84 g, 13.7 mmol, 41%).

bp: 53-56°C, 7-8 torr (lit:[90] 79-80°C, 8-10 torr). ^{1}H NMR: δ4.13 (1H, q, J = 7.0 Hz, C2-H), 2.8-3.0 (4H, m, C4,6-H_2), 2.1-2.2 (1H, m, C5-H_e), 1.8-2.0 (1H, m, C5-H_a), 1.48 (3H, d, J = 7.6 Hz, -CH_3).

2-Methyl-1,3-dithiane (109) – from acetaldehyde

Acetaldehyde (0.81 g, 18.5 mmol) and 1,3-propanedithiol (2.0 g, 18.5 mmol) were combined and stirred in a 2-necked round-bottomed flask. Gaseous hydrogen chloride was bubbled though the mixture for 1 h. The reaction mixture was poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined extracts were dried over anhydrous magnesium sulfate, filtered, and the solvent was removed *in vacuo*. The residue was distilled to give the title compound as a pale yellow oil (1.3 g, 9.6 mmol, 52%). This compound was identical in all respects to the compound **(109)** obtained as described above.

2-Methyl-1,3-dithiane-2-carboxaldehyde oxime (113)

A solution of 2-methyl-1,3-dithiane (**109**) (5 g, 37 mmol) in THF (80 ml) was stirred at –50°C in a dry-ice/acetone bath. A 15% solution of *n*-butyllithium in hexane (24 ml, 3.6 g, 56 mmol) was added over 30 min. The reaction mixture was stirred at –50°C for 1 h, then –10°C for 1 h. DMF (12 ml, 11 g, 0.16 mol) was then added in a dropwise manner, keeping the temperature between –10°C and 0°C. The reaction mixture was then stirred at 4°C for 16 h. It was then poured onto crushed ice (approx. 70 ml), separated, and the aqueous layer was extracted with ether (4 x 50 ml). The combined extracts were washed with 2M hydrochloric acid (2 x 50 ml), then 10% sodium hydroxide solution (2 x 50 ml), then dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* to give a yellow oil (5.1 g) which was purified by Kügelrohr distillation (60°C, 0.08 torr) to give a colourless oil (2.2 g). The ^{1}H NMR spectrum of this oil corresponded to that of 2-methyl-1,3-dithiane-2-carboxaldehyde (**113**).[120]

^{1}H NMR: δ9.04 (1H, s, -CHO), δ3.1 (2H, dt, J = 14 Hz, 2.4 Hz, C4,6-H_e), δ2.6 (2H, dt, J = 4.1 Hz, 14 Hz, C4,6-H_a), δ2.1 (1H, m, C5-H_e), δ1.8 (1H, m, C5-H_a), δ1.50 (3H, s, -CH_3).

A portion of this oil (2.0 g) was dissolved in a mixture of ice/water (10 ml) and ethanol (5 ml). Hydroxylamine hydrochloride (0.95 g, 14 mmol) was added, followed by the slow addition of 50% sodium hydroxide solution (2.4 ml)) in water (2 ml). The reaction was stirred for 1 h and then was washed with ether (20 ml) and the organic layer discarded. The aqueous layer was acidified to pH<5 with concentrated hydrochloric acid, forming a colourless precipitate. This was extracted with ether (4 x 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and the solvent was removed *in vacuo* to give a yellow solid. This was sublimed (50°C, 0.08 torr) to give the title compound as a white solid (2.0 g, 12 mmol, 32% yield from 2-methyl-1,3-dithiane (**109**)).

mp 148-149°C. ^{1}H NMR: δ7.88 (1H, s, -CHNOH), 7.49 (1H, s, -CHNOH), 3.11 (2H, dt, J = 3, 15 Hz, C4,6-H_e), 2.7 (2H, dt, J = 3, 15 Hz, C4,6-H_a), 2.1 (1H, m, C5-H_e), 1.8-1.9 (1H, m, C5-H_a), 1.61 (3H, s, -CH_3). ^{13}C NMR: δ153.72 (-CHNOH), 47.15 (C2), 28.01 (C4,6), 27.44 (CH_3), 24.83 (C5). MS: *m/z* 177 (bp) $[M]^+$, 162 $[M - \cdot CH_3]^+$, 160 $[M - \cdot OH]^+$, 144 $[M - SH]^+$, 133 $[M - \cdot CHNOH]^+$, 126, 118, 105, 100 $[M - \cdot CHNOH - SH]^+$, 88, 74, 59. Anal. for $C_6H_{11}NOS_2$: Calc: C: 40.65, H: 6.25, N: 7.90. Found: C: 40.92, H: 6.22, N: 7.79.

1,3-Dithiane-2-carboxaldehyde oxime (114)

1,3-Dithiane (**77**) (2.0 g, 17 mmol) was dissolved in THF (40 ml) and the reaction vessel was cooled to –30°C. *n*-Butyllithium (7.8 ml 15% solution in hexane, 1.2 g, 18 mmol) was added dropwise by syringe. The mixture was stirred at –10°C for 1 h, then DMF (5 ml, 4.7 g, 64 mmol) was added dropwise by syringe. The reaction mixture was stirred at 4°C for 16 h, then poured over ice/water (100 ml) and washed with ether (50 ml). The aqueous layer was acidified to pH < 6 with 1M hydrochloric acid solution, and then extracted with ether (4 x 50 ml). The combined organic extracts dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave the title compound as a yellow oil (1.1 g) which was used without further purification. The ^{1}H NMR spectrum of this oil was consistent with that of 1,3-dithiane-2-carboxaldehyde.[121]

^{1}H NMR: δ9.53 (1H, br s, -CHO), δ4.11 (1H, br s, C2-H), δ3.0-3.1 (2H, m, C4,6-H_e), δ2.5-2.6 (2H, m, C4,6-H_a), δ2.0-2.2 (2H, m, C5-H_2).

A portion of this oil (0.10 mg) was dissolved in a mixture of ethanol (1.0 ml) and water (2.0 ml) at 0°C. Hydroxylamine hydrochloride (0.36 g, 5.2 mmol) was added to the reaction mixture, followed by 50% aqueous sodium hydroxide solution (1.0 ml). The stirred reaction mixture was allowed to warm to room temperature over 2 h, and was then washed with ether (5 ml). The aqueous layer was acidified to pH < 5 with concentrated hydrochloric acid, and then extracted with ether (4 x 10 ml). The organic layers were dried

with anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave a mixture of 1,3-dithiane-2-carboxaldehyde *trans*-oxime and 1,3-dithiane-2-carboxaldehyde *cis*-oxime (2:1 ratio by ^{1}H NMR spectroscopy, 74 mg, 0.45 mmol, 29% from 1,3-dithiane), which were not separated.

^{1}H NMR: δ7.8-8.0 (1H major isomer (mj) + 1H minor isomer (mn), br s, -CHNOH, *cis*- and *trans*-), 7.59 (1H (mj), d, J = 5.5 Hz, -CHNOH *trans*-), 7.01 (1H (mn), d, J = 8 Hz, -CHNOH *cis*-) 5.29 (1H (mn), d, J = 8 Hz, C2-H *cis*-), 4.64 (1H (mj), d, J = 5.5 Hz, C2-H *trans*-), 2.9-3.1 (2H (mj) + 2H (mn), m, C4,6-H_e, *trans*- and *cis*-), 2.7-2.9 (2H (mj) + 2H (mn), m, C4,6-H_a, *trans*- and *cis*-), 1.9-2.2 (2H (mj) + 2H (mn), m, C5-H_2, *trans*- and *cis*-). ^{1}H NMR (d_6-benzene): δ7.6-8.2 (1H major isomer (mj) + 1H minor isomer (mn), br s, -CHNOH, *cis*- and *trans*-), 7.59 (1H (mj), d, J = 6 Hz, -CHNOH *trans*-), 6.97 (1H (mn), d, J = 8.5 Hz, -CHNOH *cis*-) 5.49 (1H (mn), d, J = 8.5 Hz, C2-H *cis*-), 4.30 (1H (mj), d, J = 6 Hz, C2-H *trans*-), 2.4-2.5 (2H (mj) + 2H (mn), m, C4,6-H_e, *trans*- and *cis*-), 2.15-2.25 (2H (mj) + 2H (mn), m, C4,6-H_a, *trans*- and *cis*-), 1.4-1.6 (2H (mj) + 2H (mn), m, C5-H_2, *trans*- and *cis*-). ^{13}C NMR: δ149.15 (CHNOH, *trans*-), 147.87 (CHNOH, *cis*-), 33.82 (C2, *trans*-), 35.85 (C2, *cis*-), 29.43 (C4,6, *trans*-), 28.51 (C4,6, *cis*-), 25.27 (C5, *trans*-), 26.09 (C5, *cis*-). MS: *m/z* 163 (bp) $[M]^+$, 146 $[M - OH]^+$, 130, 119 $[M - CHNOH]^+$, 104, 102, 91, 86, 74, 59, 46 $[CHNOH]^+$, 45. Anal. for $C_5H_9NOS_2$: Calc: C: 36.79, H: 5.56, N: 8.58. Found: C: 36.89, H: 5.37, N: 8.35

2-Butyl-1,3-dithiane (110) – From 1,3-dithiane

1,3-Dithiane (**77**) (5.0 g, 42 mmol) was dissolved in dry THF (100 ml) and the reaction vessel was cooled to –30°C. A 15% solution of *n*-butyllithium in hexane (27 ml, 4.0 g, 63 mmol) was added in a dropwise manner. The reaction was vessel was stirred at –10°C for 4 h. Butyl iodide (9.6 ml, 16 g, 0.18 mol) was added by syringe. The reaction mixture was stirred at 4°C overnight. The reaction mixture was then poured onto ice/water (100 ml) and this emulsion was extracted with ether (4 x 40 ml). The combined organic

extracts were washed with brine (50 ml), dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The resultant residue was purified by Kügelrohr distillation (60°C, 0.15 torr, lit:[122] 81-82°C 1.1 torr) to give the title compound as a colourless oil (2.51g, 14 mmol, 34%).

^{1}H NMR: δ4.05 (1H, t, J = 7 Hz, C2-H), 2.8-3.0 (4H, m, C4,6-H_2), 2.1-2.2 (1H, m, C5-H_e), 1.8-2.0 (1H, m, C5-H_a), 1.75 (2H, q, J = 7 Hz, C'1-H_2), 1.5 (2H, m, C'2-H_2), 1.33 (2H, sx, J = 7 Hz, C'3-H_2), 0.91 (3H, t, J = 7 Hz, C'4-H_3). MS: *m/z* 176 (rel. intensity: 46) $[M]^+$, 119 (bp) $[M - Bu]^+$, 87, 73. Anal. for $C_8H_{16}S_2$ Calc: C: 54.49, H: 9.15, N: 0.00. Found: C: 54.21, H: 8.89, N: 0.00.

2-Butyl-1,3-dithiane (110) – from valeraldehyde

Valeraldehyde (2.9 ml, 2.0g, 23 mmol) and 1,3-propanedithiol (1.3 ml, 2.4 g, 23 mmol) were combined in benzene (50 ml) in a round-bottomed flask equipped with a Dean-Stark apparatus. *p*-Toluenesulfonic acid (0.10 mg) was added, and the reaction mixture was heated at reflux. After the collection of approximately 0.4 ml water, the reaction mixture was cooled and washed with 5% sodium bicarbonate solution (20 ml), dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by Kügelrohr distillation (60°C, 0.15 torr, lit:[122] 81-82°C 1.1 torr) to give the title compound as a colourless oil (1.10g, 6.3 mmol, 28%). Spectral and physical data are described above.

2-Butyl-1,3-dithiane-2-carboxaldehyde (111)

A solution of 2-butyl-1,3-dithiane **(110)** (1.0 g, 5.7 mmol) in dry THF (20 ml) was cooled to –30°C in a dry-ice/acetone bath. A 15% solution of *n*-butyllithium in hexane (2.9 ml, 0.44g, 6.8 mmol) was added in a dropwise manner by syringe. The reaction mixture was stirred for 3 h at –20°C. The reaction mixture was added by syringe to a 0°C solution of dimethylformamide (1.8 ml, 1.7 g, 23 mmol) in dry THF (20 ml). This reaction mixture

was stirred at 4°C for 16 h. The reaction mixture was then poured onto ice/water (50 ml), and the resultant emulsion was extracted with ether (4 x 20 ml). The combined organic extracts were washed with 0.1M hydrochloric acid solution (20 ml) followed by brine (20 ml), then dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave the title compound as a colourless oil (1.0 g, 5.0 mmol, 87%), which was used without further purification.

^{1}H NMR: δ9.03 (1H, s, -CHO), 2.9-3.1 (2H, m, C4,6-H_e), 2.55-2.65 (2H, m, C4,6-H_a), 2.05-2.15 (1H, m, C5-H_e) 1.7-1.9 (3H, m, C5-H_a + C1'-H_2), 1.2-1.5 (4H, m, C2',3'-H_2), 0.90 (3H, t, J = 7.4 Hz, C4'-H_3). These ^{1}H NMR data are consistent with those reported in the literature.[122] Anal. for $C_9H_{16}OS_2$: Calc: C: 52.90, H: 7.89, N: 0.00. Found: C:52.48, H: 7.68, N: 0.00

2-Butyl-1,3-dithiane-2-carboxaldehyde oxime (115)

2-Butyl-1,3-dithiane-2-carboxaldehyde **(111)** (1.0 g, 5.0 mmol) was placed in a stirred solution of ethanol (10 ml) and ice/water (20 ml). To the resultant emulsion was added hydroxylamine hydrochloride (0.35 g, 5.0 mmol), followed by the dropwise addition of a 50% aqueous solution of sodium hydroxide (1.6 ml). The reaction mixture was stirred for 4 h. The reaction mixture was acidified to pH < 5 with concentrated hydrochloric acid and then extracted with ether (4 x 40 ml). The combined organic extracts were dried with anhydrous magnesium sulfate, filtered and the solvent removed to give a colourless oil. This oil was purified by flash chromatography (20% ethyl acetate in hexane) to give the title compound as colourless crystals (0.39 g, 1.8 mmol, 36%).

mp: 65-67°C. ^{1}H NMR: δ7.41 (1H, s, -CHNO<u>H</u>), 7.2 (1H, br s, -C<u>H</u>NOH), 3.0-3.15 (2H, m, C4,6-H_e), 2.6-2.7 (2H, m, C4,6-H_a), 2.1-2.2 (1H, m, C5-H_e), 1.8-1.9 (3H, m, C5-H_a + C1'-H_2), 1.4-1.55 (2H, m, C2'-H_2), 1.2-1.4 (2H, m, C3'-H_2), 0.90 (3H, t, J = 7.3 Hz, C4'-H_2). ^{13}C NMR: δ153.59 (-CHNOH), 52.77 (C2), 41.07 (C4,6), 28.17 (C1'), 26.58 (C5), 26.03 (C2'), 23.80 (C3'), 15.09 (C4'). MS: *m/z* 204 (rel. intensity: 41) $[M]^+$, 201 [M –

$H_2H_2O]^+$, 186 [M – SH]$^+$, 175 [M - $^{\cdot}$CHNOH]$^+$, 162 [M – $^{\cdot}$Bu]$^+$, 145 (bp) [M - $^{\cdot}$Bu - $^{\cdot}$OH]$^+$, 128, 119, 106, 85, 74, 71. HR MS: Calc. for $C_9H_{17}NOS_2$: 219.075158. Found: 219.075525.

2-Methyl-1,3-dithiolane-2-carboxaldehyde oxime (84)

Aqueous pyruvaldehyde solution (**82**) (40%, 21 ml, 10g, 0.14 mol) and 1,2-ethanedithiol (12 ml, 13g, 0.14 mol) were combined in benzene (75 ml) in a flask equipped with a Dean-Stark apparatus and reflux condenser. *p*-Toluenesulfonic acid (0.10 g) was added, and the reaction mixture was heated at reflux for 4 h, until 18 ml of water had been collected. On cooling, the reaction mixture was poured onto ice/water (100 ml), separated, and the organic layer washed with saturated sodium bicarbonate solution (2 x 50 ml) and water (50 ml), dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo* to give a yellow oil (18 g crude yield, 0.12 mol, 85%). A portion was distilled by Kügelrohr (40°C (0.15 torr), lit:[103] 105-108°C (20 torr), but there was evidence for decomposition on distillation. The ^{1}H NMR spectrum of this oil was consistent with that of 2-methyl-1,3-dithiolane-2-carboxaldehyde (**83**).[103] The oil could be used without further purification.

^{1}H NMR: δ9.11 (1H, s, -CHO), δ3.3-3.5 (4H, m, C4,5-H_2), δ1.77 (3H, s, -CH_3).

This oil (18 g) was dissolved in a mixture of ice/water (60 ml) and ethanol (30 ml). Hydroxylamine hydrochloride (9.0 g, 0.13 mol) was added, followed by the dropwise addition of 50% sodium hydroxide solution (24 ml) over 30 min. The reaction mixture was stirred for 1 h, then was washed with ether (50 ml) and the organic layer discarded. The aqueous layer was acidified to pH < 5 with concentrated hydrochloric acid, forming a white precipitate. This was extracted with ether (3 x 100 ml). The organic layers were collected and dried over anhydrous magnesium sulfate, then the solvent was removed *in vacuo* to give a yellow powder. Further purification by sublimation was carried out at 30°C at 0.08 torr, to give the title compound as a white solid (9.3 g, 57 mmol, 41% yield from pyruvaldehyde (**82**)).

mp: 115°C (lit:[103] 115°C). subl. < 30°C 0.08 torr (Kügelrohr). ^{1}H NMR: δ7.54 (1H, s, -CHNOH), 7.24 (variable, 1H, s, -CHNOH), 3.3-3.5 (4H, m, C4,5-H_2), 1.92 (3H, s, -CH_3). ^{13}C NMR: δ153.36 (-CHNOH), 62.30 (C2), 40.37 (C4,5), 26.75 (-CH_3). MS: *m/z* 163 (rel. intensity: 86) $[M]^+$, 148 $[M - Me]^+$, 130 $[M - SH]^+$, 119 (bp) [dithiolanyl]$^+$, 104, 91. Anal. for $C_5H_9NOS_2$: Calc: C: 36.79, H: 5.56, N: 8.58. Found: C: 36.98, H: 5.80, N: 8.74.

1-Nitro-2-propanol (123)

To a solution of nitromethane (1.6 ml, 1.8 g, 30 mmol) in water (10 ml) was added acetaldehyde (1.3 g, 30 mmol) in water (10 ml) in a dropwise manner. Sodium carbonate was added in portions to maintain a pH of ~9. The reaction was stirred for 2 h, then left standing for a further 3 h. The solution was then extracted with ether (2 x 10 ml), and the combined organic extracts were dried, filtered and the solvent was removed *in vacuo*. The resultant yellow liquid was then purified by Kügelrohr distillation (90-100°C (8 torr), lit:[126] 86-89°C (8 torr)) to give the title compound as a colourless liquid (0.64g, 6.1 mmol, 20%).

^{1}H NMR: δ4.5-4.6 (1H, m, C2-H), 4.32 (1H, ABX dd, J = 3 Hz, 13 Hz, C1-H), 4.37 (1H, ABX dd, J = 8 Hz, 13 Hz, C1-H), 2.77 (1H, br s, -OH), 1.30 (3H, d, J = 6.5 Hz, C3-H_3)

Attempted synthesis of nitroacetone (121) – from 1-nitro-2-propanol (123)

To a solution of 1-nitro-2-propanol **(123)** (1.0 g, 9.9 mmol) in water (5 ml) was added sodium dichromate (1.5 g, 5.7 mmol). A solution of concentrated sulfuric acid (1 ml) in water (1 ml) was added in a dropwise manner. The reaction mixture was stirred for 16 h, during which time no precipitation was observed. The solution was then diluted to 10 ml with water, and extracted with ether (3 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the crude product shows a

mixture of starting material and nitroacetone **(121)** in a ratio of 60:40. However, nitroacetone could not be purified by chromatography on silica or alumina; attempts resulted in decomposition.

Nitroacetone **(121)** (presumed): ^{1}H NMR: δ5.28 (2H, s, C1-H_2), 2.35 (3H, s, C3-H_3).

Attempted synthesis of nitroacetone (121) – from iodoacetone (124b)

Chloroacetone **(124a)** (0.43 ml, 0.50 g, 5.4 mmol) and sodium iodide (1.2 g, 8.1 mmol) were combined in acetone and the reaction mixture was stirred for 3 h. The reaction mixture was then filtered and the solvent was removed *in vacuo*, to give a dark brown oil (1.0 g).

Iodoacetone **(124b)**: ^{1}H NMR: δ3.82 (2H, C1-H_2), δ2.42 (3H, C3-H_3). These ^{1}H NMR data are consistent with those of iodoacetone **(124b)** presented in the literature.[148]

This oil was dissolved in ether (20 ml) was added silver nitrite (1.67g, 10.8 mmol) and the reaction mixture was stirred for 4 days at room temperature. The mixture was then filtered and the solvent removed from the filtrate *in vacuo*. The ^{1}H NMR spectrum of the crude reaction product shows a mixture of products, although signals representing nitroacetone **(121)** appear to be present at δ5.28 and δ2.35.

2-Chloromethyl-2-methyl-1,3-dioxane (125a)

Chloroacetone **(124a)** (5 ml, 5.8 g, 63 mmol), 1,3-propanediol (4.6 ml, 4.8 g, 63 mmol) and *p*-toluenesulfonic acid (0.10g) were combined in benzene (50 ml). The reaction mixture was heated at reflux in a round-bottom flask equipped with a Dean-Stark apparatus and reflux condenser for 3 h. On cooling, the benzene mixture was washed with saturated sodium bicarbonate solution (50 ml), and the aqueous layer extracted with ether (2 x 50 ml). The combined organic layers were then washed with water (50 ml), dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo* to give the

title compound as a colourless oil (4.9 g, 0.33 mol, 51%), which was used without further purification.

^{1}H NMR: δ3.9-4.0 (4H, m, C4,6-H_2), 3.62 (2H, s, -CH_2Cl), 1.65-1.85 (2H, m, C5-H_2), 1.51 (3H, s, -CH_3). This compound was unstable, and decomposed during storage at 4°C.

Attempted synthesis of 2-iodomethyl-2-methyl-1,3-dioxane (125b) – from iodoacetone (124b)

Iodoacetone **(124b)** (0.78 g, 4.2 mmol), 1,3-propanediol (0.34 ml, 0.35 g, 4.7 mmol) and *p*-toluenesulfonic acid (approx. 10 mg) were combined in benzene (20 ml). The reaction mixture was heated at reflux in a round-bottom flask equipped with a Dean-Stark apparatus and reflux condenser for 4 h. On cooling, the benzene mixture was washed with saturated sodium bicarbonate solution (10 ml), and the aqueous layer was extracted with ether (2 x 50 ml). The combined organic layers were then washed with water (10 ml), dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo* to give a brown oil. The ^{1}H NMR spectrum of the crude reaction mixture showed signals corresponding to a complex mixture of compounds; attempts at purification by washing with 10% sodium bisulfate solution resulted in decomposition of the desired product.

Attempted synthesis of 2-methyl-2-nitromethyl-1,3-dioxane (122) – from 2-chloromethyl-2-methyl-1,3-dioxane (125a)

To a solution of 2-chloromethyl-2-methyl-1,3-dioxane **(125a)** (0.81 g, 5.4 mmol) in dry ether (20 ml) was added silver nitrite (1.7 g, 10.8 mmol) and sodium iodide (approx. 0.10 g). The reaction mixture was stirred at room temperature for 7 days, and then was filtered and the solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the residue showed only signals corresponding to 2-chloromethyl-2-methyl-1,3-dioxane **(125a)**.

Attempted synthesis of 2-iodomethyl-2-methyl-1,3-dioxane (125b) – from 2-chloromethyl-2-methyl-1,3-dioxane (125a)

2-Chloromethyl-2-methyl-1,3-dioxane (**125a**) (0.81 g, 5.4 mmol) was dissolved in acetone (15 ml) and sodium iodide was added (1.2 g, 8.1 mmol). The reaction mixture was stirred at room temperature for 7 days and then filtered and the solvent was removed *in vacuo* to give a yellow/green oil. The ^{1}H NMR spectrum of the residue showed only signals corresponding to 2-chloromethyl-2-methyl-1,3-dioxane (**125a**) and iodoacetone (**124b**).

Attempted synthesis of methyl 2-methyl-1,3-dioxane-2-carboxylate (130)

Methyl pyruvate (**129**) (1.1 ml, 1.3 g, 13 mmol) and 1,3-propanediol (95 µl, 0.10 g, 1.3 mmol) were combined in dry dichloromethane (50 ml). Boron trifluoride etherate (99 µl, 0.11 g, 0.78 mmol) was added, and the reaction mixture stirred for 4 days. The solvent was removed *in vacuo*. The residue was redissolved in ethyl acetate and filtered through a large plug of silica. The solvent was removed *in vacuo*, to give a pale yellow oil (0.98 g). The residue was dissolved in ethanol (50 ml) and treated with sodium borohydride (0.36 g, 9.6 mmol). The reaction mixture was stirred for 1 h. Saturated ammonium chloride solution (50 ml) was added, and the mixture was extracted with ether (100 ml, then 50 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the residue showed signals corresponding to a mixture of methyl 2-methyl-1,3-dioxane-2-carboxylate (**130**) and a number of byproducts. The title compound could not be purified by flash chromatography (20% ethyl acetate in hexane).

^{1}H NMR (presumed, from crude reaction product): 3.9-4.1 (m, 2H, C4,6-$\underline{H}_e$),3.8-3.9 (m, 5H, C4,6-$\underline{H}_a$, -CO_2CH_3), 2.0-2.2 (m, 2H, C5-H_2) and 1.51 (3H, s, C2-CH_3).

Attempted synthesis of methyl 2,4-dimethyl-1,3-dioxane-2-carboxylate (134a)

Methyl pyruvate **(129)** (1.1 ml, 1.3 g, 13 mmol) and 1,3-butanediol **(132)** (0.12 g, 1.3 mmol) were combined in dry dichloromethane (25 ml). Boron trifluoride etherate (99 ml, 0.11 g, 0.78 mmol) was added, and the reaction mixture stirred for 4 days. The reaction mixture was diluted to 40 ml with dichloromethane and washed with 5% sodium bicarbonate solution (10 ml) and brine (10 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. Peaks corresponding to the title compound were visible in the ^{1}H NMR spectrum of the crude product mixture at δ3.82 (s, -CO_2CH_3), 1.52 (s, C2-CH_3) and 1.24 (d, J = 6 Hz, C4-CH_3). The residue was dissolved in ethyl acetate and filtered through silica, and distillation attempted. However, Kügelrohr distillation at 70-80°C (0.08 torr) resulted in decomposition of the product.

Methyl 2,5,5-trimethyl-1,3-dioxane-2-carboxylate (135)

Methyl pyruvate **(129)** (1.1 ml, 1.3 g, 13 mmol) and 2,2-dimethyl-1,3-propanediol **(133)** (0.14 g, 1.3 mmol) were combined in dry dichloromethane (25 ml). Boron trifluoride etherate (99 μl, 0.11 g, 0.78 mmol) was added, and the reaction mixture stirred for 4 days. The reaction mixture was diluted to 40 ml with dichloromethane and washed with 5% sodium bicarbonate solution (10 ml) and brine (10 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (20% ethyl acetate in hexane), to give the title compound as a colourless oil (47 mg, 0.25 mmol, 19%). This compound was not fully characterised. ^{1}H NMR: δ3.83 (3H, s, -OCH_3), 3.51 (4H, s, C4,6-H_2), 1.54 (3H, s, C2-CH_3), 1.21 (3H, s, C5-CH_3 (eq)), 0.72 (3H, C5-CH_3 (ax)).

2-(2-Chloroethyl)-2-methyl-1,3-dioxane (139)

Methyl vinyl ketone (**137**) (5.9 ml, 5.0 g, 71 mmol) was added in a dropwise manner to concentrated hydrochloric acid (7.3 ml, 2.72 g, 74 mmol), maintaining the temperature between 0°C and 5°C using an ice bath. This mixture was then partitioned between ether (50 ml) and water (50 ml), and separated. The organic layer was washed again with water (50 ml) and then dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave a colourless oil (4.4 g, 43 mmol, 60%), which was used without further purification. The ^{1}H NMR spectrum of this compound was consistent with the structure of 4-chlorobutan-2-one (**138**).

^{1}H NMR: δ3.73 (2H, t, J = 7 Hz, C4-H_2), 2.92 (2H, t, J = 7 Hz, C3-H_2), 2.21 (3H, s, C1-H_3).

A portion of this oil (2.0g, 19 mmol based on 4-chlorobutan-2-one) and 1,3-propanediol (1.4 ml, 1.4g, 19 mmol) were combined in benzene (50 ml) in a round-bottomed flask equipped with a Dean-Stark apparatus. *p*-Toluenesulfonic acid (0.10 mg) was added, and the reaction mixture was heated at reflux for 3 h. On cooling, the reaction mixture was washed with 5% aqueous sodium bicarbonate solution (50 ml), and organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave a brown oil whose composition was shown by ^{1}H NMR spectroscopy to contain starting materials and a product. Purification by Kügelrohr distillation at 50°C (0.45 torr) resulted in decomposition of this product.

2-(2-Chloroethyl)-2-methyl-1,3-dioxane (**139**): (^{1}H NMR presumed, from crude product mixture) δ3.8-4.0 (partially obscured, m, approx. 4H, -CH_2Cl overlapped with C4,6-H_a), δ3.7 (partially obscured, m, approx. 2H, C4,6-H_e), δ2.18 (m, 2H, C5-$\underline{H}_2$), 1.42 (singlet, 3H, CH_3).

2-Acetyl-1,3-dithiane (140) – from pyruvaldehyde

A 40 % w/v aqueous pyruvaldehyde (**82**) solution (5.0 ml, 2.0 g, 28 mmol) was combined with 1,3-propanedithiol (2.8 ml, 3.0 g, 18 mmol) in benzene (50 ml) in a round-bottomed flask equipped with a Dean-Stark apparatus. *p*-Toluenesulfonic acid (0.10 mg) was added and the mixture was heated at reflux for 3 h. On cooling, the reaction mixture was washed with saturated aqueous sodium bicarbonate solution (2 x 50 ml) and the organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave a brown oil which was found by ^{1}H NMR spectroscopy to contain a mixture of 2-methyl-1,3-dithiane-2-carboxaldehyde (**108**) and the title compound in a ratio of approximately 4:1 by comparison of signal intensities.

2-Acetyl-1,3-dithiane (**140**): ^{1}H NMR: δ4.28 (1H, s, C2-H), 3.22 (2H, ddd, J = 4, 10, 14 Hz, C4,6-H_e), 2.61 (2H, ddd, J = 3 6, 14, C4,6-H_a), 2.36 (3H, s, -$COCH_3$), 1.95-2.15 (2H, m, C5-H_2)

Attempted synthesis of 2-(2-Methyl-1,3-dioxan-2-yl)-1,3-dithiane (141)

1,3-Dithiane (**77**) (1.0 g, 8.3 mmol) was dissolved in dry THF (50 ml) and cooled to –78°C in a dry-ice/acetone bath. A 15% *n*-butyllithium solution in hexane (3.6 ml, 0.54 g, 8.5 mmol) was added in a dropwise manner. The reaction mixture was allowed to warm over 4 h to –30°C. Ethyl acetate (0.84 ml, 0.76 g, 8.6 mmol) was then added in a dropwise manner. The reaction was allowed to warm to room temperature over 3 h. Saturated ammonium sulfate solution (50 ml) was then added. The resultant biphasic solution was separated, and the organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the residue showed signals representing a mixture of 1,3-dithiane (**77**) and 2-acetyl-1,3-dithiane (**140**). The 1,3-dithiane (**77**) was partially removed by fractional sublimation (Kügelrohr, 40°, 0.08 torr), leaving the 2-acetyl-1,3-dithiane (**140**) as a colourless powder (0.11 g, 0.68 mmol,

8%), slightly contaminated with 1,3-dithiane (**77**) (< 15% by ^{1}H NMR), which was used without further purification.

2-Acetyl-1,3-dithiane (**140**): ^{1}H NMR: δ4.28 (1H, s, C2-H), 3.22 (2H, ddd, J = 4, 10, 14 Hz, C4,6-H_e), 2.61 (2H, ddd, J = 3, 6, 14 Hz, C4,6-H_a), 2.36 (3H, s, -$COCH_3$), 1.95-2.15 (2H, m, C5-H_2).

2-Acetyl-1,3-dithiane (**140**) (30 mg, 0.19 mmol) and 1,3-propanediol (28 mg, 0.37 mmol) were combined in benzene (12.5 ml) in a round-bottomed flask equipped with a Dean-Stark apparatus. *p*-Toluenesulfonic acid (5 mg) was added, and the reaction mixture heated at reflux for 4 h. On cooling, the reaction mixture was washed with 5% aqueous sodium bicarbonate solution (5 ml), and the organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The ^{1}H NMR spectrum of the residue indicated a complex mixture of compounds, including starting materials.

(Hydroxyimino)(2,5,5-trimethyl(1,3-dioxan-2-yl))methane (143)

1-Pyruvaldehyde *anti*-oxime (**142**) (0.30 g, 3.4 mmol), 2,2-dimethyl-1,3-propanediol (**133**) (0.52 g, 10 mmol) and trimethylsilyl chloride (2.6 ml, 2.2 g, 21 mmol) were combined in dry dichloromethane. The reaction mixture was heated at reflux and stirred for 2 days. The reaction mixture was then cooled and added to 5% sodium bicarbonate solution (15 ml) which had been cooled to 0°C using an ice bath. The mixture was then extracted with ether (4 x 15 ml). The combined organic extracts were washed with brine (20 ml), dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The resultant residue was then purified by flash chromatography (20% ethyl acetate in hexane) to give the title compound as a white powder (200 mg, 1.2 mmol, 33.5%).

mp: 62-64°C (lit:[129] 88-89°C). ^{1}H NMR: δ7.40 (1H, s, -C<u>H</u>NOH), 3.64 (2H, d, J = 11.5 Hz, C4,6-H_e), 3.44 (2H, d, J = 11.5 Hz, C4,6-H_a), 1.54 (3H, s, C2-CH_3), 1.19 (3H, s, C5-CH_3 (eq)), 0.75 (3H, s, C5-CH_3 (ax)). ^{13}C NMR: δ151.08 (-CHNOH), 96.75 (C2), 72.23

(C4,6), 29.96 (C5), 26.70 (C2-CH_3), 22.69 (C5-CH_3 (eq)), 21.92 (C5-CH_3 (ax)). MS: *m/z* 173 (rel. intensity: 2.5) $[M]^+$, 158 $[M - CH_3]^+$, 156 $[M - OH]^+$, 129 $[M - CHNOH]^+$, 88, 69, 56 (bp). Anal. for $C_8H_{15}NO_3$: Calc: C: 55.47, H: 8.73, N: 8.09, Found: C: 55.22, H: 8.52, N: 7.96

Cyclohexanecarboxaldehyde oxime (148)

Cyclohexanecarboxaldehyde **(147)** (10 ml, 9.3 g, 83 mmol) was dissolved in a mixture of ethanol (20 ml), and ice/water (20 ml). To this solution was added hydroxylamine hydrochloride (6.3 g, 91 mmol), followed by the dropwise addition of 50% aqueous sodium hydroxide solution (25 ml). The reaction was stirred for 3 h, then washed with ether. The aqueous layer was acidified to pH < 6 with concentrated hydrochloric acid, then extracted with ether (4 x 40 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave the title compound as a white solid (0.60 g, 4.7 mmol, 5.7%). The organic wash was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*, to give a mixture of the desired product and some impurities. The desired product was isolated from this mixture by distillation* to give colourless crystals (6.0 g, 47 mmol, 57%). The isomers were not separated. The structure of the isomers was assigned using the method of Karabatsos and Taller.[123]

^{1}H NMR: δ7.9 (1H minor (mn) + 1H major (mj), br s, -CHNOH (*cis*- + *trans*-)), 7.33 (1H (mj), d, J = 6 Hz, -CHNOH (*trans*-)), 6.62 (1H (mn), d, *J* = 7 Hz, -CHNOH (*cis*-)), 2.9-3.1 (1H (mn), m, α-H (*cis*-)), 2.1-2.3 (1H (mj), m, α-H (*trans*-)), 1.6-1.9 (5H (mn) + 5H (mj), m, equatorial protons (*cis*- + *trans*-)), 1.1-1.4 (5H (mn) + 5H (mj), m, axial protons (*cis*- + *trans*-)). ^{1}H NMR (d_6-benzene): δ8.8-9.2 (1H (mn) + 1H (mj), br s, -

* The melting point of the combined *cis*- and *trans*-isomers of cyclohexanecarboxaldehyde-1-oxime **(148)** (approx 30) is lower than the temperature used for distillation.

CHNOH (*cis-* + *trans-*)), 7.40 (1H (mj), d, J = 6 Hz, -CHNOH (*trans-*)), 6.44 (1H (mn), d, J = 7 Hz, -CHNOH (*cis-*)), 3.1-3.3 (1H (mn), m, α-H (*cis-*)), 2.0-2.2 (1H (mj), m, α-H (*trans-*)), 1.5-1.9 (5H (mn) + 5H (mj), m, equatorial protons (*cis-* + *trans-*)), 1.0-1.4 (5H (mn) + 5H (mj), m, axial protons (*cis-* + *trans-*)). ^{13}C NMR: δ156.48 (-CHNOH, *cis-*), 155.90 (-CHNOH, *trans-*), 38.38 (C1, *trans-*), 33.69 (C1, *cis-*), 30.06, 25.72, 25.32 (C2-6, *trans-*), 29.31, 25.73, 25.10 (C2-6, *cis-*). MS: *m/z* 127 (rel. intensity: 17) $[M]^+$, 110 $[M - OH]^+$, 98, 95, 82, 72, 67, 59 (bp), 55. Anal. for $C_7H_{13}NO$: Calc: C: 66.11, H: 10.30, N: 11.01; Found: C: 66.26, H: 10.05, N: 10.80.

Hydroximinopropane (150)

Propanal **(149)** (6.2 ml, 5.0 g, 86 mmol) was dissolved in ethanol (10 ml) and water (20 ml) and the resultant solution was cooled to 0°C in an ice bath. Hydroxylamine hydrochloride (6.0 g, 86 mmol) was added to the reaction mixture, followed by the dropwise addition of 50% aqueous sodium hydroxide solution (15 ml). The reaction mixture was stirred at room temperature for 1 h, and then was washed with ether (20 ml). The aqueous layer was acidified to pH<6 using concentrated hydrochloric acid, then extracted with ether (4 x 20 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave a mixture of *cis-* and *trans*-hydroximinopropane, as a colourless oil (3.9 g, 53 mmol, 62%) in a ratio of 1:1.1 by ^{1}H NMR spectroscopy. This substance was used without further purification.

^{1}H NMR: δ7.33 (1H major (mj), t, J = 6 Hz, C1-H (*trans-*)), 6.47 (1H minor (mn), t, J = 5 Hz, C1-H (*cis-*)), 2.38 (2H (mn), dq, J = 5 Hz, 8 Hz, C2-H_2 (*cis-*)), 2.21 (2H (mj), m, C2-H_2 (*trans-*)), 1.07 (3H (mn) + 3H (mj), closely overlapping triplets, C3-H_3 (*trans-* and *cis-*). ^{1}H NMR (d_6-benzene): 7.33 (1H (mj), t, J = 6 Hz, C1-H (*trans-*)), 6.47 (1H (mn), t, J = 5 Hz, C1-H (*cis-*)), 2.29 (2H (mn), dq, J = 5 Hz, 8 Hz, C2-H_2 (*cis-*)), 1.92 (2H (mj), dq, J = 6 Hz, 8 Hz, C2-H_2 (*trans-*)), 0.84 (3H (mn), t, J = 8 Hz, C3-H_3 (*cis-*)), 0.78 (3H (mj), t, J

= 8 Hz, C3-H_3 (*trans*-)). The ^{1}H NMR (benzene) data is consistent with those given in the literature.[123]

1-Chloro-1-(hydroxyimino)acetone (151)

To a solution of chloroacetone (**124a**) (9.2 g, 0.10 mol) in ether (100 ml) was added *i*-pentyl nitrite (12 g, 0.11 mol) followed by concentrated hydrochloric acid (10 ml, 0.10 mol). The reaction was stirred for 16 h in a round bottomed flask equipped with a calcium chloride drying tube, during which time the original brown solution changed colour to pale yellow. The solvent was removed *in vacuo* and the residue was recrystallised twice from carbon tetrachloride to give the title compound as a white powder (4.4 g, 36 mmol, 36%). mp: 102-104°C (lit:[104] 107-108°C). ^{1}H NMR: δ8.80 (1H, br s, -CClNOH), 2.51 (3H, s, -$COCH_3$). ^{13}C NMR: δ176.93 (C=O), 140.01 (-CClNOH), 25.88 (-CH_3).

Experimental – Chapter 5

Attempted mercuric(II) acetate oxidation of 2-methyl-1,3-dithiane-2-carboxaldehyde oxime (113)

2-Methyl-1,3-dithiane-2-carboxaldehyde oxime (**113**) (0.10 g, 0.56 mmol), ethyl *trans*-cinnamate (**70**) (0.10 g, 0.56 mmol) and mercuric(II) acetate (0.18g, 0.56 mmol) were combined in ethanol (10 ml) and the mixture was heated at reflux for 3 h. The solvent was removed *in vacuo*. ^{1}H NMR analysis of the crude product mixture indicated that only signals corresponding to the starting materials were present.

Attempted mercuric(II) acetate oxidation of 2,6-dichlorobenzaldoxime (91)

2,6-Dichlorobenzaldoxime (**91**) (0.21 g, 1.1 mmol), ethyl *trans*-cinnamate (**70**) (0.19 g, 1.1 mmol) and mercuric(II) acetate (0.35 g, 1.1 mmol) were combined in ethanol (5 ml) and the mixture was heated at reflux and stirred for 3 h. The solvent was then removed *in vacuo*. ^{1}H NMR analysis of the crude product mixture indicated that only signals corresponding to the starting materials were present.

Lead(IV) tetraacetate oxidation of 2,6-dichlorobenzaldoxime (91)

2,6-Dichlorobenzaldoxime (**91**) (0.10 g, 0.52 mmol) and ethyl *trans*-cinnamate (**70**) (93 mg, 0.52 mmol) in dichloromethane (5 ml) were cooled to –78°C in a dry-ice/acetone bath. Lead(IV) tetraacetate (0.27 g, 0.61 mmol) in dichloromethane (5 ml) was added over 30 min by dropping funnel, while keeping the temperature below –70°C. The mixture was stirred at –78°C for 1 h, then triethylamine (0.17 ml, 0.12 g, 2 mmol) was added by syringe and the reaction vessel warmed to room temperature. Ether (20 ml) and anhydrous magnesium sulfate(0.24 g) were added to the reaction mixture and the mixture was stirred vigorously for 5 min. The reaction mixture was then filtered, washed with saturated sodium bicarbonate solution (10 x 5 ml), dried over anhydrous magnesium sulfate and the

solvent was removed *in vacuo* to give a yellow oil. ^{1}H NMR signals corresponding to the chemical shifts reported in the literature[84] for the isomer ethyl 3-(2,6-dichlorophenyl)-5-phenylisoxazole-4-carboxylate **(72b)** at δ6.25 (d, J = 9.0 Hz), and 4.58 (d, J = 9.0 Hz), and for the isomer ethyl 3-(2,6-dichlorophenyl)-4-phenylisoxazole-5-carboxylate **(73b)** at δ5.30 (br d), 5.25 (br d). These compounds were not isolated.

^{1}H NMR study of the stability of 2-methyl-1,3-dithiane-2-carbonitrile *N*-oxide (104)

To a solution of 2-methyl-1,3-dithiane-2-carboxaldehyde oxime **(113)** (29 mg, 0.16 mmol) and methyl benzoate (23.4 mg) in *d*-chloroform (1.0 ml) was added lead(IV) tetraacetate (71 mg, 0.16 mmol). The reaction mixture was stirred for 5 min before adding saturated sodium bicarbonate solution (approx. 1 ml). The organic layer was separated and filtered though a small plug of silica into an NMR tube. ^{1}H NMR spectroscopy showed signals corresponding to the title compound. The yield of the title compound was calculated at 10 mg (59 μmol, 37%) by comparison of signal intensities of the nitrile oxide and methyl benzoate in the ^{1}H NMR spectrum. ^{1}H NMR spectra were recorded daily for 8 days, with further spectra being recorded at t = 11 and 17 days. Approximately 50% of the nitrile oxide **(104)** remained in solution after 8 days.

^{1}H NMR: δ3.25 (2H, m, C4,6-H$_e$), 2.90 (2H, m, C4,6-H$_a$), 2.24 (1H, m, C5-H$_e$), 1.8-1.9 (4H, m, C5-H$_e$ + -CH$_3$). IR: 2279 cm^{-1} (strong, C≡N).

Attempted lead(IV) tetraacetate oxidation of 1,3-dithiane-2-carboxaldehyde oxime (114)

To a solution of 1,3-dithiane-2-carboxaldehyde oxime **(114)** (10 mg, 61 μmol) and methyl benzoate (14.8 mg) in dry dichloromethane (2 ml) was added lead(IV) tetraacetate (30 mg, 67 μmol). The reaction mixture was stirred for 5 min before adding saturated sodium bicarbonate solution (approx. 1 ml). The organic layer was separated and the solvent was removed *in vacuo*, and the residue was taken up in *d*-chloroform (1 ml).

Methyl acrylate (2 drops) was added to the solution. Only signals corresponding to methyl acrylate were visible by ^{1}H NMR spectroscopy.

^{1}H NMR study of the stability of of 2-butyl-1,3-dithiane-2-carbonitrile *N*-oxide (106)

To a solution of 2-butyl-1,3-dithiane-2-carboxaldehyde oxime (**115**) (30 mg, 0.14 mmol) in *d*-chloroform (0.8 ml) was added lead(IV) tetraacetate (60 mg, 0.14 mmol). The reaction mixture was stirred for 5 min before adding saturated sodium bicarbonate solution (approx. 1 ml). The organic layer was separated and filtered though a small plug of silica into an NMR tube. Methyl benzoate (22.4 mg) was added to the NMR tube. ^{1}H NMR spectroscopy showed signals corresponding to the title compound. The yield of the title compound was calculated at 13 mg (61 μmol, 43%) by comparison of signal intensities of the nitrile oxide and methyl benzoate. ^{1}H NMR spectra were recorded at t = 0, 1 day, 9 days and 6 weeks. No decomposition was observed during this time.

^{1}H NMR: δ3.25 (2H, m, C4,6-H$_e$), 2.89 (2H, m, C4,6-H$_a$), 2.25 (1H, m, C5-H$_e$), 2.01 (2H, m, C1'-H$_2$), 1.91 (1H, m, C5-H$_e$), 1.66 (2H, m, C2'-H$_2$), 1.39 (2H, sx, J = 7 Hz, C3'-H$_2$), 0.92 (3H, t, J = 7 Hz, C4'-H$_3$). IR: 2277 cm^{-1} (strong, C≡N).

^{1}H NMR study of the stability of 2-methyl-1,3-dithiolane-2-carbonitrile *N*-oxide (81)

To a solution of 2-methyl-1,3-dithiolane-2-carboxaldehyde oxime (**84**) (35 mg, 0.21 mmol) and methyl benzoate (19.4 mg) in *d*-chloroform (1 ml) was added lead(IV) tetraacetate (0.10 g, 0.23 mmol). The reaction mixture was stirred for 5 min before adding saturated sodium bicarbonate solution (approx. 1 ml). The organic layer was separated and filtered though a small plug of silica into an NMR tube. ^{1}H NMR spectroscopy showed signals corresponding to the title compound. The yield of the title compound was calculated at 4.1 mg (25 μmol, 12%) by comparison of the signal intensities of nitrile oxide

and methyl benzoate. A ^{1}H NMR spectrum recorded after 18 h showed < 5% of the nitrile oxide (**81**) remained.

^{1}H NMR: δ3.57 (4H, m, C4,5-H_2), 2.09 (3H, s, -CH_3)

Chloro(hydroxyimino)(2,5,5-trimethyl(1,3-dioxan-2-yl))methane (159)

(Hydroxyimino)(2,5,5-trimethyl(1,3-dioxan-2-yl))methane (**143**) (0.57 g, 3.3 mmol) was dissolved in dry DMF (5 ml) in a 2-necked round-bottomed flask equipped with a thermometer. To this solution was added *N*-chlorosuccinimide (0.53 g, 4.0 mmol) in 5 portions over 20 min. The temperature of the reaction was maintained below 37°C by immersion of the reaction vessel in an ice/water bath. After the reaction temperature had stabilised, the reaction mixture was stirred at 10°C for 1 h. The reaction mixture was then poured into cold water (30 ml) and this biphasic system was extracted with ether (3 x 20 ml). The combined organic extracts were washed with water (4 x 20 ml), dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The impurities in the reaction mixture were removed by Kügelrohr distillation (50-60°C, 1.5 torr), leaving the title compound as a white powder (0.28 g, 1.34 mmol, 41%).

mp: 129-131 (lit:[129] 112-114°C). ^{1}H NMR: δ7.91 (1H, s, v, -CClNOH), 3.59 (2H, d, J = 11 Hz, C4,6-H_e), 3.45 (2H, d, J = 11 Hz, C4,6-H_a), 1.60 (3H, s, C2-CH_3), 1.22 (3H, s, C5-CH_3 (equatorial)), 0.74 (3H, s, C5-CH_3 (axial)). ^{13}C NMR: δ140.48 (-CClNOH), 98.67 (C2), 72.29 (C4,6), 29.33 (C5), 26.95 (C2-CH_3), 22.79 (C5-CH_3 (equatorial)), 21.87 (C5-CH_3 (axial)).

^{1}H NMR study of the stability of 2,5,5-trimethyl-1,3-dioxane-2-carbonitrile *N*-oxide (160) – triethylamine generation

Chloro(hydroxyimino)(2,5,5-trimethyl(1,3-dioxan-2-yl))methane (**159**) (15 mg, 72 μmol) and methyl benzoate (15.0 mg) were combined in *d*-chloroform (0.5 ml). To this solution was added a solution of triethylamine (15 μl, 11 mg, 80 μmol) in *d*-chloroform (0.5

ml). The reaction mixture was shaken to ensure thorough mixing of the contents, and a ^{1}H NMR spectrum was recorded. The yield of nitrile oxide was calculated at 12 mg (75 μmol, 104%) by comparison of signal intensities of nitrile oxide and methyl benzoate. ^{1}H NMR spectra were recorded at t=0, 24 h and 3 days. After 24 h, less than 10% of the nitrile oxide was observed by ^{1}H NMR spectroscopy. After 3 days, no signals corresponding to the nitrile oxide were visible by ^{1}H NMR spectroscopy.

^{1}H NMR: δ3.71 (2H, d, J = 11 Hz, C4,6-H$_e$), 3.57 (2H, d, J = 11 Hz, C4,6-H$_a$), 1.79 (3H, s, C2-CH$_3$), 1.16 (3H, s, C5-CH$_3$ (equatorial)) 0.80 (3H, s, C5-CH$_3$ (axial)). IR: 2260 cm^{-1} (strong, C≡N).

^{1}H NMR study of the stability of 2,5,5-trimethyl-1,3-dioxane-2-carbonitrile *N*-oxide (160) – sodium bicarbonate generation

Chloro(hydroxyimino)(2,5,5-trimethyl(1,3-dioxan-2-yl))methane **(159)** (15 mg, 72 μmol) was dissolved in *d*-chloroform (0.5 ml). This solution was washed with saturated sodium bicarbonate solution (1 ml) and the organic layer was filtered though a small plug of silica. A ^{1}H NMR spectrum was recorded, showing signals corresponding to the title compound and an unidentified product. After 3 days, no signals corresponding to the nitrile oxide were observed by ^{1}H NMR spectroscopy. ^{1}H NMR data for the nitrile oxide **(160)** were as described above.

IR study of the stability of Adamantanecarbonitrile *N*-oxide (22)

To a solution of adamantanylchloro(hydroxyimino)methane **(161)** (53 mg, 0.25 mmol) in dry dichloromethane (1 ml) was added triethylamine (34 μl, 25 mg, 0.25 mmol). The IR spectrum of this reaction mixture was recorded at 10 min intervals for 3 h, then at 1 day intervals for 3 days, then at 6 and 14 days. After 3 days, the signal intensity of the nitrile oxide signal at 2290 cm^{-1} is at about 50% of the same signal at t = 0. After 6 days, the signal is comparable to the detection limits of the instrument.

Chlorocyclohexyl(hydroxyimino)methane (162)

Cyclohexanecarboxaldehyde oxime **(148)** (1.0 g, 7.8 mmol) was dissolved in dry DMF (10 ml) in a 2-necked round-bottomed flask equipped with a thermometer. To this solution was added *N*-chlorosuccinimide (1.0 g, 8.2 mmol) in 5 portions over 15 min. The temperature of the reaction mixture was maintained at < 35°C by immersion in an ice bath when necessary. The reaction mixture was stirred for 30 min after the temperature had stabilised, and then partitioned between ether (60 ml) and 0.1M hydrochloric acid solution (20 ml). The layers were separated and the organic layer was washed with 0.1M hydrochloric acid solution (20 ml) and brine (20 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave the title compound as colourless crystals (1.1 g, 7.0 mmol, 90%). This compound was found to be unstable and was thus used without further purification.

^{1}H NMR: δ8.2 (1H, br s, -CClNOH), 2.4-2.5 (1H, m, α-H), 1.6-2.0 (5H, m, equatorial protons), 1.2-1.5 (5H, m, axial protons)

^{1}H NMR study of the stability of cyclohexanecarbonitrile *N*-oxide (87)

A solution of chlorocyclohexyl(hydroxyimino)methane **(162)** (13 mg, 80 μmol) in *d*-chloroform (1.0 ml) was washed with saturated sodium bicarbonate solution (3 ml). The organic layer was separated and filtered though a small plug of silica. To this solution was added methyl benzoate (10.7 mg). The reaction mixture was shaken to ensure thorough mixing of the contents and ^{1}H NMR spectra were recorded. The yield of nitrile oxide was calculated at 7.0 mg (56 μmol, 70%) by comparison of signal intensities of nitrile oxide and methyl benzoate. ^{1}H NMR spectra were recorded at hourly intervals for 4 h, then on a daily basis. After 3 days, 50% of nitrile oxide remained.

^{1}H NMR: δ2.7-2.9 (1H, m, α-H), 1.2-2.0 (10H, m, Cy).

IR study of the stability of cyclohexanecarbonitrile *N*-oxide (87)

To a stirred solution of chlorocyclohexyl(hydroxyimino)methane **(162)** (0.48 g, 3.0 mmol) in dry dichloromethane (12 ml) was added triethylamine (4.1 ml, 0.30 g, 3.0 mmol). IR spectra were recorded at t = 0 and 28 h. After 28 h, the nitrile oxide absorbance, initially visible as a strong signal at 2302 cm^{-1}, was not observed.

1-Chloro-1-(hydroxyimino)propane (164)

Hydroximinopropane **(150)** (0.10 g, 1.4 mmol) was dissolved in dry DMF (2 ml). To this solution was added *N*-chlorosuccinimide (0.20 g, 1.5 mmol). The temperature of the reaction was maintained below 37°C by immersion of the reaction vessel in an ice/water bath. After the reaction temperature had stabilised, the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then poured into cold water (10 ml) and this biphasic system was extracted with ether (4 x 10 ml). The combined organic extracts were washed with 0.1M hydrochloric acid solution (10 ml) and brine (10 ml), dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave the title compound as a colourless oil (95 mg, 0.88 mmol, 63 %). This compound was extremely unstable and decomposed upon standing for > 2 h. As such, it was used immediately for the cycloaddition experiments without further purification.

^{1}H NMR: δ8.0 (1H, br s, -CClNOH), 2.56 (2H, q, J = 7 Hz, C2-H_2), 1.23 (3H, t, J = 7 Hz).

^{1}H NMR study of the stability of propanenitrile *N*-oxide (17)

A solution of 1-chloro-1-(hydroxyimino)propane **(164)** (13 mg, 80 μmol) in *d*-chloroform (1 ml) was washed with saturated sodium bicarbonate solution (2 ml). The organic layer was separated and filtered though a small plug of silica. To this solution was added methyl benzoate (10.9 mg). The reaction mixture was shaken to ensure thorough mixing of the contents and ^{1}H NMR spectra were recorded. The yield of the title

compound was calculated at 5.6 mg (79 μmol, 99%) by comparison of signal intensities of nitrile oxide and methyl benzoate. ^{1}H NMR spectra were recorded at hourly intervals for 4 h, then on a daily basis. After 24 h, 50% of the initial amount of nitrile oxide remained. After 5 days, no signal corresponding to the nitrile oxide was observed.

^{1}H NMR: δ2.56 (2H, q, J = 7.5 Hz, CH_2), 1.31 (3H, t, J = 7.5 Hz, CH_3).

^{1}H NMR study of the stability of 2-Oxopropanenitrile *N*-oxide (61)

To a solution of 1-chloro-1-(hydroxyimino)acetone **(151)** (9.7 mg, 80 μmol) in *d*-chloroform (1.0 ml) was added triethylamine (15 μl, 11 mg, 80 μmol). The reaction mixture was shaken to ensure thorough mixing of the contents, and a ^{1}H NMR spectrum was recorded within 5 min of the addition of triethylamine. The ^{1}H NMR spectrum showed only signals corresponding to 3,4-bisacetylfuroxan **(165)** and triethylamine. The reaction was repeated on a larger scale; the furoxan was unstable and decomposed while flash chromatography was attempted.

^{1}H NMR (furoxan): 2.62 (1H, s, C4-$COCH_3$), 2.71 (1H, s, C5-$COCH_3$). IR: 1800 (medium, C=O) and 1700 cm^{-1} (strong, C=O), 1610 cm^{-1} (strong) (C=N-O) and 1490 cm^{-1} (medium, C=NO_2). These data are consistent with those presented in the literature for 3,4-bisacetylfuroxan.[135]

Experimental – Chapter 6

Synthesis of 3-(2-methyl-1,3-dithian-2-yl)-4,5-dihydroisoxazoles

General procedure

To a solution of 2-methyl-1,3-dithiane-2-carboxaldehyde oxime (0.30 g, 1.7 mmol) in dry dichloromethane (80 ml) was added lead tetraacetate (0.75 g, 1.7 mmol). The reaction mixture was stirred for 5 min and then was filtered. The filtrate was washed with saturated sodium bicarbonate solution (20 ml), separated and the aqueous layer was extracted with ether (2 x 10 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and filtered through silica. To this filtrate was added dipolarophile (3.4 mmol), and the reaction mixture was stirred for 5 days. The solvent was then removed *in vacuo*, and the residue was purified by flash chromatography (20% ethyl acetate in hexane).

*Methyl 3-(2-methyl-1,3-dithian-2-yl)-4,5-dihydroisoxazole-5-carboxylate (**155**)*

Dipolarophile: Methyl acrylate (**34**). Yield: 0.25 g (0.94 mmol, 55%). Appearance: colourless crystals. mp: 84°C. ^{1}H NMR: δ5.03 (1H, dd, J = 7, 10 Hz, C5-H), 3.74 (3H, s, -OCH_3), 3.3-3.4 (ABX multiplet, C4-H_2), 3.2-3.3 (1H, m, dithiane C4-H_e), 3.0-3.1 (1H, m, dithiane C6-H_e), 2.6-2.7 (2H, m, dithiane C4,6-H_a), 2.0-2.1 (1H, m, dithiane C5-H_e), 1.7-1.9 (1H, m, dithiane C5-H_a), 1.61 (3H, s, -CH_3). ^{13}C NMR: δ170.43 (-$\underline{C}O_2CH_3$), 160.71 (C3), 78.38 (C5), 52.65 (-$CO_2\underline{C}H_3$), 45.10 (dithiane C2), 38.44 (C4), 27.91 (dithiane C4), 27.55 (dithiane C6), 27.05 (-CH_3), 24.05 (dithiane, C5). MS: *m/z* 261 (bp) $[M]^+$, 246 $[M - CH_3]^+$, 228 $[M - SH]^+$, 202 $[M - CO_2CH_3]^+$, 187, 168, 159.9, 140, 133 [methyldithianyl]$^+$, 100, 74, 59. Anal. for $C_{10}H_{15}NO_3S_2$: Calc: C: 45.96, H: 5.78, N: 5.36. Found: C: 46.09, H: 6.16, N: 5.10.

*[3-(2-Methyl-1,3-dithian-2-yl)-4,5-dihydroisoxazol-5-yl]methyl acetate (**167**)*

Dipolarophile: Allyl acetate (**166**). Yield: 0.19 g (0.69 mmol, 40%). Appearance: pale yellow oil. ^{1}H NMR: δ4.90 (1H, m, C5-H), 4.18 (1H, ABX dd, J = 4, 11 Hz,

-OCH_2-), 4.13 (1H, ABX dd, J = 5, 11 Hz, -OCH_2-), 3.1-3.3 (3H, m, C4-H dd, J = 11, 17 Hz, overlapping dithiane C4,6-H_e signals (2 x multiplet)), 2.96 (1H, dd, J = 7, 17 Hz, C4-H), 2.7 (2H, m, C4,6-H_a), 2.1 (4H, m, includes CH_3CO_2- and C5-H_e), 1.9 (1H, m, C5-H_a), 1.69 (3H, s, -CH_3). ^{13}C NMR: δ170.78 ($CH_3\underline{C}O_2$-), 160.83 (C3), 78.53 (C5), 64.99 (C5-CH_2O-), 45.48 (C4), 36.72 (dithiane C2), 29.70 (CH_3CO_2-), 27.99 (dithiane C4), 27.28 (dithiane C6), 24.26 (dithiane CH_3), 20.81 (dithiane C5), MS: *m/z* 275 (rel. intensity: 91) $[M]^+$, 260 $[M - \cdot CH_3]^+$, 242 (bp) $[M - SH]^+$, 214, 202 $[M - CH_3CO_2CH_2\cdot]^+$, 141, 133 [methyldithianyl]$^+$, 128, 100 $[CH_2{=}CHCH_2O_2CCH_3]^+$, 73, 59 $[CH_3CO_2\text{-}]^+$. Anal. for $C_{11}H_{17}NO_3S_2$: Calc: C: 47.98, H: 6.22, N: 5.09, Found: C: 47.57, H: 6.62, N: 4.98. This compound is unstable and decomposes slowly to give an orange/brown oil.

*Methyl 5-methyl-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-5-carboxylate (**168**)*

Dipolarophile: Methyl methacrylate(**42**). Yield: 0.13 g (0.48 mmol, 28%). Appearance: colourless oil. ^{1}H NMR: δ3.79 (3H, s, -OCH_3), 3.62 (1H, d, J = 17 Hz, C4-H), 3.2 (2H, dq, J = 13, 3 Hz, dithiane C4,6-H_e), 2.98 (1H, d, J = 17 Hz, C4-H), 2.6-2.7 (2H, m, C4,6-H_a), 2.1 (1H, m, C5-H_e), 1.8-1.9 (1H, m, C5-H_a), 1.65 (3H, s, dithiane –CH_3), 1.64 (3H, s, C5-CH_3). ^{13}C NMR: δ172.28 (-$\underline{C}O_2CH_3$), 161.14 (C3), 86.60 (C5), 52.94 (-$CO_2\underline{C}H_3$), 45.41 (C4), 44.33 (dithiane C2), 27.94 (dithiane C4), 27.72 (dithiane C6), 27.15 (dithiane –CH_3), 24.20 (dithiane C5), 23.09 (C5-CH_3). MS: *m/z* 275 (rel. intensity: 47) $[M]^+$, 260 $[M - \cdot CH_3]^+$, 242, 216 $[M - \cdot CH_3CO_2]^+$, 202, 142 [M – methyldithianyl]$^+$, 133 [methyldithianyl]$^+$, 100 $[CH_2{=}C(CH_3)CO_2CH_3]^+$, 74, 59 (bp) $[CH_3CO_2]^+$. Anal. for $C_{11}H_{17}NO_3S_2$: Calc: C: 47.98, H: 6.22, N: 5.09. Found: C: 48.33, H: 6.46, N: 5.05.

*Methyl 4,5-*trans*-5-(methoxycarbonyl)-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-4-carboxylate (**170**)*

Dipolarophile: Dimethyl fumarate (**169**). Yield: 0.35 g (1.1 mmol, 64%). Appearance: Colourless oil. ^{1}H NMR: δ5.31 (1H, d, J = 5 Hz, C5-H), 4.44 (1H, d, J = 5 Hz, C4-H), 3.82 (3H, s, C5-CO_2CH_3), 3.77 (3H, s, C4-CO_2CH_3), 3.36 (1H, ddd, J = 3, 13,

17 Hz, dithiane C4-H_e), 3.10 (1H, ddd, J = 3, 13, 15 Hz, dithiane C6-H_e), 2.63 (2H, m, dithiane C4,6-H_a), 2.1 (1H, m, dithiane C5-H_e), 1.8 (1H, m, dithiane C5-H_a), 1.71 (3H, s, -CH_3). ^{13}C NMR: δ168.93 (C5-$\underline{C}O_2CH_3$), 168.81 (C4-$\underline{C}O_2CH_3$), 157.67 (C3), 83.28 (C5), 56.50 (C4), 56.24 (C5-$CO_2\underline{C}H_3$), 53.16 (C4-$CO_2\underline{C}H_3$), 44.89 (dithiane C2), 29.69 (dithiane C4), 28.11 (dithiane C6), 27.04 (-CH_3), 23.81 (dithiane C5). MS: *m/z* 319 (rel. intensity: 71) $[M]^+$, 304 $[M - CH_3]^+$, 286 (bp) $[M - SH]^+$, 275, 260 $[M - CO_2CH_3]^+$, 245, 242, 200, 186 [M - methyldithianyl]$^+$, 166, 154, 133 [methyldithianyl]$^+$, 106, 100 Anal. for $C_{12}H_{17}NO_5S_2$: Calc: C: 45.13, H: 5.36, N: 4.39. Found: C: 44.84, H: 5.61, N: 4.60.

*Methyl 4,5-*cis*-5-(methoxycarbonyl)-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-4-carboxylate (**172**)*

Dipolarophile: Dimethyl maleate (**171**). Yield: 0.11 g (0.33 mmol, 44%). Appearance: needlelike colourless crystals. mp: 124°C (decomposes). ^{1}H NMR: δ5.29 (1H, d, J = 11 Hz, C5-H), 4.34 (1H, d, J = 11 Hz, C4-H), 3.82 (3H, s, C5-CO_2CH_3), 3.70 (3H, s, C4-CO_2CH_3), 3.51 (1H, m, dithiane C4-H_e), 3.0 (1H, m, dithiane C6-H_e), 2.55-2.7 (2H, m, dithiane C4,6-H_a), 2.07 (1H, m, dithiane C5-H_e), 1.85 (1H, m, dithiane C5-H_a), 1.72 (3H, s, -CH_3). ^{13}C NMR: δ168.74 (C5-$\underline{C}O_2CH_3$), 168.61 (C4-$\underline{C}O_2CH_3$), 159.65 (C3), 83.76 (C5), 56.46 (C4), 53.96 (C4,5-$CO_2\underline{C}H_3$ – coincidence of signals confirmed by HETCOR experiment), 45.90 (dithiane C2), 29.29 (dithiane C4), 28.86 (dithiane C6), 28.32 (-CH_3), 24.75 (dithiane C5). MS: *m/z* 319 (bp) $[M]^+$, 304 $[M - CH_3]^+$, 286 $[M - SH]^+$, 260 $[M - CO_2CH_3]^+$, 245, 232, 213, 200, 186 [M – methyldithianyl]$^+$, 166, 154, 158, 133 [methyldithianyl]$^+$, 126, 113, 106, 100. Anal. for $C_{12}H_{17}NO_5S_2$: Calc: C: 45.13, H: 5.36, N: 4.39. Found: C: 44.75, H: 5.22, N: 4.58.

*Methyl 4,5-*trans*-5-methyl-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-4-carboxylate (**173**) and methyl 4,5-*trans*-4-methyl-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-5-carboxylate (**174**)*

Dipolarophile: Methyl crotonate (**49**). Methyl 4,5-*trans*-5-methyl-3-(2-methyl-(1,3-dithian-2-yl))-4,5-dihydroisoxazole-4-carboxylate (**173**): Yield: 0.16 g (0.57 mmol,

33%). Appearance: colourless oil. ^{1}H NMR: δ4.98 (1H, br p (dq), J = 6 Hz, C5-H), 3.71 (4H, overlapping singlet and doublet (J = 6 Hz), -OCH_3 and C4-H), 3.29 (1H, ddd, J = 3, 13, 15 Hz, dithiane C4-H_e), 3.11 (1H, ddd, J = 3, 13, 15 Hz, dithiane C6-H_e), 2.6 (2H, m, dithiane C4,6-H_a) 2.1 (1H, m, dithiane C5-H_a), 1.8 (1H, m, C5-H_a), 1.68 (3H, s, dithiane CH_3), 1.34 (3H, d, J = 6 Hz, C5-CH_3). ^{13}C NMR: δ170.55 (-$\underline{C}O_2CH_3$), 157.79 (C3), 83.80 (C5), 59.88 (-$CO_2\underline{C}H_3$), 53.33 (C4), 46.01 (dithiane C2), 28.64 (dithiane C4,6), 27.69 (dithiane –CH_3), 24.51 (dithiane C5), 21.22 (C5-CH_3). MS: *m/z* 275 (rel. intensity: 86) $[M]^+$, 260 $[M - CH_3]^+$, 242 (bp) $[M - SH]^+$, 214, 201, 186, 177, 160, 154, 144, 133 [methyldithianyl]$^+$, 126, 125, 118, 100 $[CH_3CH{=}CHCO_2CH_3]^+$. Anal. for $C_{11}H_{17}NO_3S_2$: Calc: C: 47.98, H: 6.22, N: 5.09. Found: C: 47.66, H: 6.02, N: 5.09

Methyl 4,5-*trans*-4-methyl-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-5-carboxylate (**174**): yield: 9.0 mg (34 μmol, 1.9%). Appearance: Colourless oil. ^{1}H NMR: δ4.66 (1H, d, J = 4 Hz, C5-H), 3.78 (3H, s, -OCH_3), 3.64 (1H, dq, J = 4, 7 Hz, C4-H), 3.35 (1H, m, dithiane C4-H_e), 3.04 (1H, m, dithiane C6-H_e), 2.6 (2H, m, dithiane C4,6-H_a), 2.1 (1H, m, dithiane C5-H_e), 1.8 (1H, m, dithiane C5-H_a), 1.73 (3H, s, dithiane CH_3), 1.45 (3H, d, J = 7 Hz, C4-CH_3). MS: *m/z* 275 (rel. intensity: 78) $[M]^+$, 260 $[M - CH_3]^+$, 242 $[M - SH]^+$, 228, 214, 202, 186, 174, 142 (bp) [M – methyldithianyl]$^+$, 133 [methyldithianyl]$^+$, 74, 59 $[CO_2CH_3]^+$. HR MS: Calc. for $C_{11}H_{17}NO_3S_2$: 275.064987 Found: 275.064796.

*Ethyl 4,5-*trans*-3-(2-methyl(1,3-dithian-2-yl))-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (**175**) and ethyl 4,5-*trans*-3-(2-methyl(1,3-dithian-2-yl))-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (**176**)*

Dipolarophile: Ethyl cinnamate (**70**). Ethyl 4,5-trans-3-(2-methyl(1,3-dithian-2-yl))-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (**175**): Yield: 0.29 g (0.84 mmol, 49%). Appearance: colourless oil. ^{1}H NMR: δ7.2-7.4 (5H, m, Ar H), 5.90 (1H, d, J = 7 Hz, C5-H), 4.08 (1H, d, J = 7 Hz, C4-H), 4.23 (2H, q, J = 7 Hz, -$OC\underline{H}_2CH_3$), 3.31 (1H, m, dithiane C4-H_e), 3.15 (1H, m, dithiane C6-H_e), 2.64 (2H, m, dithiane C4,6-H_a), 2.1 (1H, m,

C5-H_e), 1.85 (1H, m, C5-H_a), 1.67 (3H, s, -CH_3), 1.36 (3H, t, J = 7 Hz, -$OCH_2\underline{C}H_3$). ^{13}C NMR: δ169.38 (-$\underline{C}O_2CH_2CH_3$), 157.16 (C3), 139.19 (Ar C1), 128.90 (*o*-Ar C), 128.63 (*m*-Ar C), 125.37 (*p*-Ar C), 88.18 (C5), 62.22 (C4), 61.26 (-$CO_2\underline{C}H_2CH_3$), 45.41 (dithiane C2), 28.10 (dithiane C4,6), 27.09 (-CH_3), 23.93 (dithiane C5), 13.92 (-$CO_2CH_2\underline{C}H_3$). MS: *m/z* 351 (rel. intensity: 40) $[M]^+$, 336 $[M - CH_3]^+$, 318.1 $[M - SH]^+$, 275, 260, 242, 204, 149, 141, 133 [methyldithianyl]$^+$, 105 (bp) $[PhCO]^+$, 100. Anal. for $C_{17}H_{21}NO_3S_2$: Calc: C: 58.09, H: 6.02, N: 3.99. Found: C: 58.00, H: 6.22, N: 3.90.

Ethyl 4,5-*trans*-3-(2-methyl(1,3-dithian-2-yl))-4-phenyl-4,5-dihydroisoxazole-5-carboxylate **(176)**: Yield: 25 mg (71 μmol, 4%). Appearance: colourless oil. ^1H NMR: δ7.2-7.4 (5H, m, Ar H), 4.90 (1H, d, J = 3 Hz, C5-H), 4.72 (1H, d, J = 3 Hz, C4-H), 4.28 (q, 2H, J = 7 Hz, -$OC\underline{H}_2CH_3$), 3.57 (1H, m, dithiane C4-H_e, 3.02 (1H, m, dithiane C6-H_e), 2.55-2.75 (2H, m, dithiane C4,6-H_a), 2.1 (1H, m, C5-H_e), 1.8 (1H, m, C5-H_a), 1.32 (3H, t, J = 7 Hz, -$OCH_2\underline{C}H_3$), 1.16 (3H, s, -CH_3). MS: *m/z* 351 (rel. intensity: 58) $[M]^+$, 336 $[M - CH_3]^+$, 318 $[M - SH]^+$, 304, 277, 228, 216, 204, 189, 176 $[PhCH{=}CHCO_2CH_2CH_3]^+$, 172, 149, 133 [methyldithianyl]$^+$, 105, 85, 59 (bp). HR MS: Calc. for $C_{17}H_{21}NO_3S_2$: 351.096287. Found: 351.096375.

2-Methyl-1,3-dithiane-2-carbonitrile *N*-oxide (104) – ^1H NMR cycloaddition experiments

*Preparation of Stock Solution and Reaction of 2-Methyl-1,3-dithiane-2-carbonitrile N-Oxide (**104**) with Ethyl trans-Cinnamate (**70**)*

To a solution of 2-methyl-1,3-dithiane-2-carboxaldehyde oxime **(113)** (0.30 g, 1.7 mmol) in *d*-chloroform (15 ml) was added methyl benzoate as an internal standard (169 mg), followed by lead(IV) tetraacetate (0.78 g, 1.8 mmol). The reaction mixture was stirred for 5 min then washed with a saturated solution of sodium bicarbonate (2 x 5 ml), dried over anhydrous magnesium sulfate and filtered though a large plug of silica. The

plug was washed with *d*-chloroform (2 x 2 ml), and the solution was rediluted to 15 ml with *d*-chloroform to replace solvent lost during the filtration.

A sample of the stock solution (1.5 ml) described above was placed in an NMR tube. To this tube was added ethyl *trans*-cinnamate (19 μl, 20 mg, 0.11 mmol). Using the integration of the signals in the ^{1}H NMR spectrum representing ethyl *trans*-cinnamate (**70**) at t=0 (*i.e.*, before any measurable cycloaddition has taken place) as a secondary standard, the quantity of methyl benzoate remaining after filtration was found to be 14.2 mg in the 1.5 ml aliquot. The amount of nitrile oxide was calculated to be 12 mg (69 mmol, 41% yield), and was assumed to be identical for the remaining tubes.

After 2 days at room temperature, the combined yield of the cycloadducts ethyl 4,5-*trans*-3-(2-methyl(1,3-dithian-2-yl))-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (**175**) and ethyl 4,5-*trans*-3-(2-methyl(1,3-dithian-2-yl))-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (**176**) was calculated at 56% by comparison of the intensities of signals representing the isoxazolines with those of methyl benzoate. The ratio of the isomers was calculated at 3:1 by comparison of the integrations of the C5-proton signals.

General procedure

To an NMR tube containing 1.5 ml (12 mg, 69 mmol nitrile oxide, 14.2 mg methyl benzoate) of the stock solution described above was added dipolarophile (0.11 mmol). The tube was inverted repeatedly to ensure thorough mixing. The yield of cycloadduct was determined by comparison of the ^{1}H NMR signal intensities of the isoxazolines with methyl benzoate.

Methyl 3-(2-methyl-1,3-dithian-2-yl)-4,5-dihydroisoxazole-5-carboxylate (155)

Dipolarophile: Methyl acrylate (**34**). Yield: 83%. ^{1}H NMR data are described above.

[3-(2-Methyl-1,3-dithian-2-yl)-4,5-dihydroisoxazol-5-yl]methyl acetate (167)

Dipolarophile: Allyl acetate (**166**). Yield: 85%. ^{1}H NMR data are described above.

*Methyl 5-methyl-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-5-carboxylate (**168**)*

Dipolarophile: Methyl methacrylate (**42**). Yield: 80%. ^{1}H NMR data are described above.

*Methyl 4,5-cis-5-(methoxycarbonyl)-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-4-carboxylate (**172**)*

Dipolarophile: Dimethyl maleate (**171**). Yield: 73%. ^{1}H NMR data are described above.

*Methyl 4,5-trans-5-(methoxycarbonyl)-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-4-carboxylate (**170**)*

Dipolarophile: Dimethyl fumarate (**169**). Yield: 78%. ^{1}H NMR data are described above.

*Methyl 4,5-trans-5-methyl-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-4-carboxylate (**173**) and methyl 4,5-trans-4-methyl-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-5-carboxylate (**174**)*

Dipolarophile: Methyl Crotonate (**49**). Yield (Combined): 58% (5:1 ratio of regiosomers). ^{1}H NMR data are described above.

Methyl 3-(2-butyl-1,3-dithian-2-yl)-4,5-dihydroisoxazole-5-carboxylate (179)

To a solution of 2-butyl-1,3-dithiane-2-carboxaldehyde oxime (0.18 g, 0.82 mmol) in dry dichloromethane (15 ml) was added lead tetraacetate (0.36 g, 0.82 mmol). The reaction mixture was stirred for 5 min and then was filtered. The filtrate was washed with saturated sodium bicarbonate solution (10 ml), then brine (10 ml). The organic layer was dried over anhydrous magnesium sulfate and filtered through silica. To this filtrate was added methyl acrylate (74 µl, 70 mg, 0.82 mmol), and the reaction mixture was stirred for 2 days. The solvent was then removed *in vacuo*, and the residue was purified by flash chromatography (10% ethyl acetate in hexane) to give the title compound as a clear oil (62 mg, 0.20 mmol, 25%).

^{1}H NMR: δ5.11 (1H, dd, J = 7, 10 Hz, C5-H), 3.80 (3H, s, -OCH_3), 3.37 (2H, ABX multiplet, C4-H_2), 3.1-3.3 (2H, m, C4,6-H_e), 2.6-2.7 (2H, m, C4,6-CH_a), 2.1-2.2 (1H, m, C5-H_e), 1.8-1.95 (3H, m, C5-H_a and butyl C1-H_2), 1.2-1.5 (4H, m, butyl C2,C3-H_2), 0.91 (3H, t, J = 7 Hz, butyl C4-H_3). ^{13}C NMR: δ171.22 (-$\underline{C}O_2CH_3$), 160.56 (C3), 79.17 (C5), 53.31 (-$CO_2\underline{C}H_3$), 40.33 (dithiane C2), 33.42 (C4), 28.25 (dithiane C4,6), 28.00 (butyl C1), 26.37 (butyl C2), 25.55 (dithiane C5), 23.30 (butyl C3), 14.33 (butyl C4). MS: *m/z* 303 $[M]^+$, 270 $[M - SH]^+$, 260, 246 (bp) $[M - {}^{\cdot}Bu]^+$, 175 [butyldithanyl]$^+$, 174, 145, 101, 85, 71, 59 $[CO_2CH_3]^+$, 58. Anal. for $C_{13}H_{21}NO_3S_2$: Calc: C: 51.46, H: 6.98, N: 4.62. Found: C: 51.61, H: 7.13, N: 4.76.

Ethyl 4,5-*trans*-3-(2-butyl(1,3-dithian-2-yl))-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (180) and ethyl 4,5-*trans*-3-(2-butyl(1,3-dithian-2-yl))-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (181)

To a solution of 2-butyl-1,3-dithiane-2-carboxaldehyde oxime (2.0 g, 9.1 mmol) in dry dichloromethane (50 ml) was added lead tetraacetate (4.1 g, 9.1 mmol). The reaction mixture was stirred for 5 min and then was filtered. The filtrate was added to saturated sodium bicarbonate solution (50 ml). This gave an emulsion which was filtered through a small plug of silica. The resultant biphasic mixture was separated and the aqueous layer was extracted with ether (2 x 50 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and filtered through silica. To this filtrate was added dipolarophile (3.4 mmol), and the reaction mixture was stirred for 5 days. The solvent was then removed *in vacuo*, and the residue was purified by flash chromatography (10% ethyl acetate in hexane) to give ethyl 4,5-*trans*-3-(2-butyl(1,3-dithian-2-yl))-5-phenyl-4,5-dihydroisoxazole-4-carboxylate **(180)** as a colourless oil (0.37 g, 10%) and ethyl 4,5-*trans*-3-(2-butyl(1,3-dithian-2-yl))-4-phenyl-4,5-dihydroisoxazole-5-carboxylate **(181)** as colourless crystals (35 mg, 1%).

Ethyl 4,5-*trans*-3-(2-butyl(1,3-dithian-2-yl))-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (**180**): ^{1}H NMR: δ7.3-7.4 (5H, m, Ar H), 5.95 (1H, d, J = 6 Hz, C5-H), 4.20 (2H, q, J = 7 Hz, -OC$\underline{H}_2$CH$_3$), 3.91 (1H, d, J = 6 Hz, C4-H), 3.42 (1H, dt, J = 3, 13.5 Hz, dithiane C4-H$_e$), 3.05 (1H, dt, J = 3, 13.5 Hz, dithiane C6-H$_e$), 2.55-2.75 (2H, m, dithiane C4,6-H$_a$), 2.1-2.2 (1H, m, dithiane C5-H$_e$), 1.8-1.95 (3H, m, dithiane C5-H$_a$ overlapped with butyl C1-H$_2$), 1.5-1.7 (2H, butyl C2-H$_2$), 1.32 (3H, t, J = 7 Hz, -OCH$_2$C$\underline{H}_3$), 1.1-1.3 (2H, m, butyl C3-H$_2$), 0.73 (3H, t, J = 7 Hz, butyl C4-H$_3$). ^{13}C NMR: δ169.27 (-$\underline{C}$O$_2$CH$_2$CH$_3$), 156.22 (C3), 139.26 (Ar C1), 128.74 (*o*-Ar C), 128.42 (*m*-Ar C), 125.10 (*p*-Ar C), 88.09 (C5), 62.04 (-CO$_2\underline{C}$H$_2$CH$_3$), 61.77 (C4), 39.53 (dithiane C2), 27.88 (dithiane C4,6), 27.64 (butyl C1), 25.39 (dithiane C5), 24.53 (butyl C2), 22.49 (butyl C3), 13.79 (-CO$_2$CH$_2\underline{C}$H$_3$), 13.54 (butyl C4). MS: *m/z* 393 (bp) [M]$^{+}$, 360 [M – SH]$^{+}$, 336 [M - ^{t}Bu], 319, 259, 228, 175 [butyldithianyl]$^{+}$, 141, 126, 115, 105 [PhCO]$^{+}$, 106, 77 [Ph]$^{+}$.

Ethyl 4,5-*trans*-3-(2-butyl(1,3-dithian-2-yl))-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (**181**): mp 81-84°C. ^{1}H NMR: δ7.5-7.6 (5H, m, Ar H), 5.02 (1H, d, J = 3 Hz, C5-H), 4.81 (1H, d, J = 3 Hz, C4-H), 4.28 (2H, q, J = 7 Hz, -OC$\underline{H}_2$CH$_3$), 3.25-3.4 (1H, m, dithiane C4-H$_e$), 3.0-3.1 (1H, m, dithiane C6-H$_e$), 2.55-2.75 (2H, m, C4,6-H$_a$), 2.1-2.2 (1H, m, C5-H$_e$), 1.8 –1.95 (1H, m, C5-H$_a$), 1.55-1.45 (2H, m, butyl C1-H$_2$), 1.15-1.4 (m, 5H, -OCH$_2$C$\underline{H}_3$ overlapped with butyl C2-H$_2$), 0.7-0.1 (m, butyl C3-H$_2$), 0.62 (3H, t, J = 7 Hz, butyl C4-H$_3$). ^{13}C NMR: δ169.85 –$\underline{C}$O$_2$CH$_2$CH$_3$), 162.02 (C3), 137.99 (Ar C1), 128.99 (*o*-Ar C), 128.26 (*m*-Ar C), 127.67 (*p*-Ar C), 87.76 (C5), 61.87 (–CO$_2\underline{C}$H$_2$CH$_3$), 58.55 (C4), 39.77 (dithiane C2), 27.72 (dithiane C4,6), 27.16 (butyl C1), 25.44 (dithiane C5), 24.81 (butyl C2), 22.20 (butyl C3), 14.05 (–CO$_2$CH$_2\underline{C}$H$_3$), 13.44 (butyl C4). MS: *m/z* 393 (93) [M]$^{+}$, 360 [M – SH]$^{+}$, 336 [M - ^{t}Bu]$^{+}$, 320 [M - ^{t}CO$_2$CH$_2$CH$_3$]$^{+}$, 216, 175 [butyldithianyl]$^{+}$, 142 [butyldithianyl – SH]$^{+}$, 127, 119, 106, 101, 91, 73 [CO$_2$CH$_2$CH$_3$]$^{+}$. HR MS: Calc. for C$_{20}$H$_{27}$NO$_3$S$_2$: 393.143238. Found: 393.143110

2-Butyl-1,3-dithiane-2-carbonitrile *N*-oxide (106) – ^{1}H NMR cycloaddition experiments

Reaction of 2-butyl-1,3-dithiane-2-carbonitrile N-*oxide (**106**) with methyl acrylate (**34**)*

To a solution of 2-butyl-1,3-dithiane-2-carboxaldehyde oxime (**115**) (37 mg, 0.17 mmol) in *d*-chloroform (1.0 ml) was added lead(IV) tetraacetate (75 mg, 0.17 mmol). The reaction mixture was stirred for 5 min before adding saturated sodium bicarbonate solution (approx. 1 ml). The organic layer was separated and filtered though a small plug of silica into an NMR tube. Methyl acrylate (**34**) (15 μl, 15 mg, 0.17 mmol) and methyl benzoate (20.1 mg) were added to the NMR tube. The yield of nitrile oxide was assumed to be the same as when the nitrile oxide was generated alone (43%, 73 μmol – see above). ^{1}H NMR spectra were recorded at t = 0, 1 day, 3 days, 9 days and 6 weeks. The yield of the cycloadduct methyl 3-(2-butyl-1,3-dithian-2-yl)-4,5-dihydroisoxazole-5-carboxylate (**179**) was calculated by comparison of signal intensities of the isoxazoline and methyl benzoate in the ^{1}H NMR spectrum as 17 mg (63 μmol, 86%). No changes in the signal intensities of the standard or the cycloadduct were observed after 3 days.

Reaction of 2-butyl-1,3-dithiane-2-carbonitrile N-*oxide (**106**) with ethyl* trans-*cinnamate (**70**)*

To a solution of 2-butyl-1,3-dithiane-2-carboxaldehyde oxime (**115**) (37 mg, 0.17 mmol) in *d*-chloroform (1.0 ml) was added lead(IV) tetraacetate (75 mg, 0.17 mmol). The reaction mixture was stirred for 5 min saturated sodium bicarbonate solution (approx. 1 ml) was added. The organic layer was separated and filtered though a small plug of silica into an NMR tube. Ethyl *trans*-cinnamate (**70**) (28 μl, 30 mg, 0.17 mmol) and methyl benzoate (17.6 mg) were added to the NMR tube. The initial ^{1}H NMR spectrum showed poor formation of the nitrile oxide. The yield of nitrile oxide could be calculated from the t = 0 spectrum as the cycloaddition to the dipolarophile was slow. The yield was calculated at 11 mg (49 μmol, 29%) by comparison of signal intensities of the isoxazolines and methyl benzoate. ^{1}H NMR spectra were recorded at t = 0, 1 day, 3 days, 9 days and six

weeks. No change in signal intensities was observed after 3 days. The total yield of the cycloadducts was calculated as 15 mg (39 μmol, 80%) by comparison of signal intensities of the isoxazoline and methyl benzoate in the ^{1}H NMR spectrum. The ratio of isomers was 3:2 by comparison of the C5 isoxazoline signal intensities.

Methyl 3-(2-methyl-1,3-dithiolan-2-yl)-4,5-dihydroisoxazole-5-carboxylate (182)

To a solution of dichloromethane (3 ml) containing 2-methyl-1,3-dithiolane-2-carboxaldehyde oxime **(84)** (0.10 g, 0.61 mmol) and methyl acrylate **(34)** (55 μl, 53 mg, 0.61 mmol) was added a solution of lead(IV) tetraacetate (0.30 g, 0.67 mmol) in dichloromethane (2 ml) is a dropwise manner over a period of 30 min. The reaction mixture was then stirred for 2 h and then partitioned between ice/water (20 ml) and ether (20 ml). The organic layer was separated and the aqueous layer extracted with ether (4 x 20 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified using flash chromatography (20% ethyl acetate in hexane) to give the title compound as a pale yellow oil (23 mg, 93 μmol, 15%). This compound decomposed within days to a brown oil.

^{1}H NMR: δ5.09 (1H, dd, J = 8, 11 Hz, C5-H), 3.81 (3H, s, -CO_2CH_3), 3.58 (2H, ABX multiplet, J = 8, 11 Hz, C4-H_2), 3.35-3.50 (4H, m, dithiolane-H), 2.07 (3H, s, dithiolane-CH_3).

2,5,5-Trimethyl-1,3-dioxane-2-carbonitrile *N*-oxide (160) – ^{1}H NMR cycloaddition experiments

General procedure

A stock solution of chloro(hydroxyimino)(2,5,5-trimethyl(1,3-dioxan-2-yl))methane **(159)** (90 mg, 0.43 mmol) and methyl benzoate (82 μl, 90 mg) in *d*-chloroform (3 ml) was prepared. Aliquots of this solution (0.50 ml, 72 μmol, 15 mg chlorooxime, 15 mg methyl benzoate) were then transferred to NMR tubes. To each

aliquot was added 0.50 ml of a 0.16 M solution of triethylamine (80 μmol). The tubes were shaken to ensure thorough mixing. ^{1}H NMR spectra were recorded at t = 0, 1, 2 and 3 days. Yields were calculated by comparison of signal intensities of the isoxazolines and methyl benzoate. Structures were assigned by analogy with known compounds.

Reaction of 2,5,5-trimethyl-1,3-dioxane-2-carbonitrile N-*oxide* ***(160)*** *with methyl acrylate* ***(34)***

Yield: 94%. ^{1}H NMR: δ5.04 (1H, t, J = 9 Hz, C5-H), 3.77 (3H, s, -OCH_3). 3.64 (1H, br d, C4-H), 3.54 (1H, br d, C4-H), 3.44 (2H, d, J = 9 Hz, C4,6-H_e), 3.25 (2H, d, J = 9 Hz, C4,6-H_a), 1.54 (3H, s, dioxane C2-CH_3), 1.13 (3H, s, dioxane C5-CH_3 (equatorial)), 0.74 (3H, s, dioxane C5-CH_3 (axial)). The chemical shifts of the isoxazoline resonances are consistent with similar compounds reported in the literature[78, 139] and in the present study. The C5-H resonance of a 5-methoxycarbonylisoxazoline is generally in the region of δ5.0 - 5.2. The C4-resonances are generally in the region of δ3.2 - 3.7.

Reaction of 2,5,5-trimethyl-1,3-dioxane-2-carbonitrile N-*oxide* ***(160)*** *with ethyl* trans-*cinnamate* ***(70)***

Yield: < 10%. Ratio of isomers: 5:3. Only the signals at 5.63 (1H, d, C5-H, major isomer), 4.46 (1H, d, C4-H, major isomer), 4.98 (1H, d, C5-H, minor isomer) and 4.52 (1H, d, C4-H, minor isomer) were used to identify the products. This assignment is consistent with the shifts of similar compounds reported in the literature[78, 139] and in the present study. The C5-H resonance of a 4-ethoxycarbonyl-5-phenylisoxazoline is generally in the region of δ5.9 - 6.2. The C4-resonance is generally in the region of δ3.9 - 4.5. The C5-H resonance of a 5-ethoxycarbonyl-4-phenylisoxazoline is generally in the region of δ4.8 -5.1. The C4-resonance is generally in the region of δ4.5 - 4.9.

Adamantanecarbonitrile N-oxide (22) – ^{1}H NMR cycloaddition experiments

Reaction of adamantanecarbonitrile N-*oxide (22) with methyl acrylate (34)*

Adamantanylchloro(hydroxyimino)methane **(161)** (17 mg, 80 μmol) was dissolved in *d*-chloroform (1.0 ml) in an NMR tube. To this tube was added methyl acrylate **(34)** (14 μl, 14 mg, 0.16 mmol), methyl benzoate (8.4 mg) and triethylamine (11 μl, 8.1 mg, 80 μmol), in that order. The NMR tube was inverted repeatedly to ensure thorough mixing of the constituents. ^{1}H NMR spectra were recorded at t = 0 and 6 days. The yield of the cycloadduct methyl 3-adamantyl-4,5-dihydroisoxazole-5-carboxylate was calculated by comparison of signal intensities of the isoxazoline and methyl benzoate as 12 mg (47 μmol, 59%).

This compound was not purified but was identified using the isoxazoline resonances in their ^{1}H NMR spectra by analogy with similar compounds in the literature[78, 139] and in the present study. The C5-H resonance of a 5-methoxycarbonylisoxazoline is generally in the region of δ5.0 - 5.2. The C4-resonances are generally in the region of δ3.2 - 3.7.

^{1}H NMR: δ4.93 (1H, dd, J = 7 Hz, 10 Hz, C5-H), 3.20 (2H, ABX multiplet, J = 7 Hz, 10 Hz, C4-H_2).

Reaction of adamantanecarbonitrile N-*oxide (22) with ethyl* trans-*cinnamate (70)*

Adamantanylchloro(hydroxyimino)methane **(161)** (17 mg, 80 μmol) was dissolved in *d*-chloroform (1.0 ml) in an NMR tube. To this tube was added ethyl *trans*-cinnamate **(70)** (27 μl, 28 mg, 0.16 mmol), methyl benzoate (15.1 mg) and triethylamine (11 μl, 8.1 mg, 80 μmol), in that order. The NMR tube was inverted repeatedly to ensure thorough mixing of the constituents. ^{1}H NMR spectra were recorded at t = 0 and 6 days. The yield of the cycloadducts ethyl 4,5-*trans*-3-adamantanyl-5-phenyl-4,5-dihydroisoxazole-4-carboxylate **(187)** and ethyl 4,5-*trans*-3-adamantanyl-4-phenyl-4,5-dihydroisoxazole-5-carboxylate **(188)** was calculated by comparison of signal intensities of the isoxazoline and methyl benzoate as 10 mg (29 μmol, 36%). The ratio of isomers was 3.8:1. These

compounds were not isolated but were identified using the isoxazoline resonances in their ^{1}H NMR spectra by analogy with similar compounds in the literature[78, 139] and in the present study. The C5-H resonance of a 4-ethoxycarbonyl-5-phenylisoxazoline is generally in the region of δ5.9 - 6.2. The C4-resonance is generally in the region of δ3.9 - 4.5. The C5-H resonance of a 5-ethoxycarbonyl-4-phenylisoxazoline is generally in the region of δ4.8 - 5.1. The C4-resonance is generally in the region of δ4.5 - 4.9.

Major isomer **(187)**: ^{1}H NMR: δ5.66 (1H, d, J = 6.0 Hz, C5-H), 3.93 (1H, d, J = 6.0 Hz, C4-H).

Minor isomer **(188)**: ^{1}H NMR: δ4.69 (1H, d, J = 2.7 Hz, C5-H), 4.52 (1H, d, J = 2.7 Hz, C4-H).

Methyl 3-cyclohexyl-4,5-dihydroisoxazole-5-carboxylate (189)

Cyclohexanecarboxaldehyde oxime **(148)** (0.10 g, 0.78 mmol) was dissolved in dry DMF (2 ml) in a 2-necked round-bottomed flask equipped with a thermometer. To this solution was added *N*-chlorosuccinimide (0.10 g, 0.82 mmol). The temperature of the reaction mixture was maintained at < 35°C by immersion in an ice bath when necessary. The reaction mixture was stirred for 30 min after the temperature had stabilised. Methyl acrylate **(34)** (0.14 ml, 0.13g, 0.15 mmol) was added, followed by triethylamine (0.11 ml, 79 mg, 0.78 mmol). The reaction mixture was stirred for 24 hours, then partitioned between ether (30 ml) and 0.1 M hydrochloric acid solution (10 ml). The layers were separated and the organic layer was washed with 0.1 M hydrochloric acid solution (10 ml) and brine (10 ml). The organic layer was then dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography (10% ethyl acetate in hexane) to give the title compound as a colourless oil (135 mg, 82%).

^{1}H NMR: δ4.97 (1H, t, J = 9 Hz, C5-H), 3.79 (3H, s, -OCH_3), 3.22 (2H, d, J = 9 Hz, C4-H_2), 2.4-2.5 (1H, m, C3-CH), 1.65-1.95 (5H, m, cyclohexane H_e), 1.15-1.45 (5H, m,

cyclohexane H_a). ^{13}C NMR: δ172.18 (-$\underline{C}O_2CH_3$), 163.31 (C3), 77.77 (C5), 53.79 (-OCH_3), 40.41 (C4), 38.02 (C5-$\underline{C}H$), 31.41, 31.31 (C2,6), 26.84, 26.71, 26.45 (C3-5). MS: *m/z* 212 (rel. intensity) 43 $[M+H]^+$, 152 $[M - {}^{\cdot}CO_2CH_3]^+$, 143, 130, 122, 89, 83 (bp) $[Cy]^+$, 70, 61, 55. Anal. for $C_{11}H_{17}NO_3$: Calc: C: 62.54, H: 8.11, N: 6.63. Found: C: 62.61, H: 8.29, N: 6.64.

Cyclohexanecarbonitrile *N*-oxide (87) – ^{1}H NMR cycloaddition experiments

General procedure

A stock solution of chlorocyclohexyl(hydroxyimino)methane **(162)** (90 mg, 0.56 mmol) and methyl benzoate (82 μl, 90 mg) in *d*-chloroform (3 ml) was prepared. 0.50 ml aliquots of this stock solution were then transferred to NMR tubes. To each aliquot was added 0.50 ml of a 0.21 M solution of triethylamine. The tubes were shaken to ensure thorough mixing. ^{1}H NMR spectra were recorded at daily intervals for 6 days. Yields were calculated by comparison of signal intensities of the isoxazolines and methyl benzoate.

Methyl 3-cyclohexyl-4,5-dihydroisoxazole-5-carboxylate (189)

Dipolarophile: Methyl acrylate **(34)**. Yield: 100%.

*Methyl 4,5-*trans*-3-cyclohexyl-5-methyl-4,5-dihydroisoxazole-4-carboxylate (190) and methyl 4,5-*trans*-3-cyclohexyl-4-methyl-4,5-dihydroisoxazole-5-carboxylate (191)*

Dipolarophile: Methyl crotonate **(49)**. Yield: 70%. Ratio of regioisomers: 3:1. These compounds were not isolated but were identified using the isoxazoline resonances in their ^{1}H NMR spectra by analogy with similar compounds in the literature[78, 139] and in the present study. The C5-H resonance of a 4-methoxycarbonyl-5-methylisoxazoline is generally in the region of δ4.9 - 5.2. The C4-resonance is generally in the region of δ3.6 - 4.1. The C5-H resonance of a 5-methoxycarbonyl-4-methylisoxazoline is generally in the region of δ4.6 - 4.8. The C4-resonance is generally in the region of δ3.4 - 4.0.

Methyl 4,5-*trans*-3-Cyclohexyl-5-methyl-4,5-dihydroisoxazole-4-carboxylate **(190)** – ^{1}H NMR: δ4.82 (1H, br p (dq), C5-H), 3.61 (1H, d, J = 8 Hz, C4-H).

Methyl 4,5-*trans*-3-Cyclohexyl-4-methyl-4,5-dihydroisoxazole-5-carboxylate **(191)** – ^{1}H NMR: δ4.48 (1H, d, J = 5.9 Hz), 3.45 (1H, m, C4-H)

Ethyl 4,5-trans-3-cyclohexyl-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (192) and ethyl 4,5-trans-3-Cyclohexyl-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (193)

Dipolarophile: Ethyl *trans*-cinnamate **(70)**. Yield (combined): 71%. Ratio of regioisomers: 5:2. These compounds were not isolated but were identified using the isoxazoline resonances in their ^{1}H NMR spectra by analogy with similar compounds in the literature[78, 139] and in the present study. The C5-H resonance of a 4-ethoxycarbonyl-5-phenylisoxazoline is generally in the region of δ5.9 - 6.2. The C4-resonance is generally in the region of δ3.9 - 4.5. The C5-H resonance of a 5-ethoxycarbonyl-4-phenylisoxazoline is generally in the region of δ4.8 - 5.1. The C4-resonance is generally in the region of δ4.5 - 4.9.

Ethyl 4,5-*trans*-3-Cyclohexyl-5-phenyl-4,5-dihydroisoxazole-4-carboxylate **(192)** ^{1}H NMR: δ5.80 (1H, d, J = 8 Hz, C5-H), 4.01 (1H, d, J = 8 Hz, C4-H)

Ethyl 4,5-*trans*-3-cyclohexyl-4-phenyl-4,5-dihydroisoxazole-5-carboxylate **(193)** ^{1}H NMR: δ 4.80 (1H, d, J = 4.5 Hz, C5-H), 4.55 (1H, d, J = 4.5 Hz, C4-H)

Methyl 3-ethyl-4,5-dihydroisoxazole-5-carboxylate (103) and methyl 3-ethyl-4,5-dihydroisoxazole-4-carboxylate (194)

Hydroximinopropane **(150)** (1.0 g, 14 mmol) was dissolved in dry DMF (20 ml). To this solution was added *N*-chlorosuccinimide (1.7 g, 14 mmol) in 4 portions over 30 min. The temperature of the reaction was maintained below 37°C by immersion of the reaction vessel in an ice/water bath. After the reaction temperature had stabilised, methyl acrylate (2.5 ml, 2.3 g, 27 mmol) was added, followed by triethylamine (2.0 ml, 1.4 g, 14 mmol). The reaction mixture was stirred for 24 h, then partitioned between ether (60 ml) and 1M hydrochloric acid solution (20 ml). The layers were separated and the organic layer was washed with 1M hydrochloric acid solution (20 ml) and brine (20 ml). The

organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was partially purified by flash chromatography (20% ethyl acetate in hexane) to give a mixture of methyl 3-ethyl-4,5-dihydroisoxazole-5-carboxylate **(103)** and methyl 3-ethyl-4,5-dihydroisoxazole-4-carboxylate **(194)** as a clear oil (0.65 mg). This mixture was purified by flash chromatography (20% ethyl acetate in hexane) to give methyl 3-ethyl-4,5-dihydroisoxazole-5-carboxylate **(103)** as a clear oil (0.32 g, 2.0 mmol, 15%) and methyl 3-ethyl-4,5-dihydroisoxazole-4-carboxylate **(194)** as a clear oil (43 mg, 0.27 mmol, 2%).

Methyl 3-ethyl-4,5-dihydroisoxazole-5-carboxylate **(103)**: ^{1}H NMR: δ5.01 (1H, t, J = 9 Hz, C5-H), 3.81 (3H, s, -OCH_3), 3.24 (2H, d, J = 9 Hz, C4-H_2), 2.41 (2H, q, J = 7.5 Hz, C3-C$\underline{H}_2$$CH_3$), 1.20 (3H, t, J = 7.5 Hz, C3-CH_2C$\underline{H}_3$). ^{13}C NMR: δ170.92 (-$\underline{C}O_2CH_3$), 159.32 (C3), 76.73 (C5), 52.62 (-$CO_2\underline{C}H_3$), 40.72 (C4), 20.79 (C3-$\underline{C}H_2CH_3$), 10.66 (C3-$CH_2\underline{C}H_3$). MS: *m/z* 158 (rel. intensity 61) $[M + H]^+$, 140, 130, 112, 102, 98 $[M - CO_2CH_3]^+$, 70 (bp), 59 $[CO_2CH_3]^+$, 55. Anal. for $C_7H_{11}NO_3$: Calc: C: 53.49, H: 7.05, N: 8.91. Found: C: 53.44, H: 7.02, N: 9.14.

Methyl 3-ethyl-4,5-dihydroisoxazole-4-carboxylate **(194)**: ^{1}H NMR: δ4.63 (1H, t (apparent), J = 8.5 Hz, C5-H), 4.47 (1H, dd, J = 8.5, 11 Hz, C4-H_a), 4.05 (1H, dd, J = 8, 11 Hz, C4-H_b), 3.78 (3H, s, -OCH_3), 2.53 (1H, dq, J = 8, 6 Hz, C3-C$\underline{H}_{(a)}$$CH_3$), 2.35 (1H, dq, J = 8, 16 Hz, C3-C$\underline{H}_{(b)}$$CH_3$), 1.21 (3H, t, J = 8, C3-CH_2C$\underline{H}_3$). ^{13}C NMR: δ169.08 (-$\underline{C}O_2CH_3$), 156.66 (C3), 71.19 (C5), 54.97 (-$CO_2\underline{C}H_3$), 52.71 (C4), 20.37 (C3-$\underline{C}H_2CH_3$), 10.58 (C3-$CH_2\underline{C}H_3$). MS: 158 $[M + H]^+$, 157 (rel. intensity 87) $[M]^+$, 126 $[M - OCH_3]^+$, 112, 98 $[M - CO_2CH_3]^+$, 96, 85, 70 $[M - CO_2CH_3 - CH_2CH_3]^+$, 68 (bp) , 59 $[CO_2CH_3]^+$, 55. Anal. for $C_7H_{11}NO_3$: Calc: C: 53.49, H: 7.05, N: 8.91. Found: C: 53.62, H: 6.95, N: 8.85.

Propanenitrile *N*-oxide (17) – ^{1}H NMR cycloaddition experiments

Reaction of propanenitrile N-*oxide (17) with methyl acrylate (34)*

1-Chloro-1-(hydroxyimino)propane **(164)** (8.5 mg, 79 μmol) was dissolved in *d*-chloroform (1.0 ml) in an NMR tube. To this tube was added methyl acrylate **(34)** (14 μl, 14 mg, 0.16 mmol), methyl benzoate (6.5 mg) and triethylamine (11 μl, 8.1 mg, 80 μmol), in that order. The NMR tube was inverted repeatedly to ensure thorough mixing of the constituents. ^{1}H NMR spectra were recorded at t = 1, 2 and 3 days. The yield of the cycloadduct methyl 3-ethyl-4,5-dihydroisoxazole-5-carboxylate **(103)** was calculated by comparison of signal intensities of the isoxazoline and methyl benzoate as 8.6 mg (55 μmol, 69%). The yield of the minor isomer, methyl 3-ethyl-4,5-dihydroisoxazole-4-carboxylate, was below the detection limits of the spectrometer.

Reaction of propanenitrile N-*oxide (17) with ethyl* trans-*cinnamate (70)*

1-Chloro-1-(hydroxyimino)propane **(164)** (9.0 mg, 83 μmol) was dissolved in *d*-chloroform (1.0 ml) in an NMR tube. To this tube was added ethyl *trans*-cinnamate **(70)** (27 μl, 28 mg, 0.16 mmol), methyl benzoate (8.6 mg) and triethylamine (11 μl, 8.1 mg, 80 μmol), in that order. The NMR tube was inverted repeatedly to ensure thorough mixing of the constituents. ^{1}H NMR spectra were recorded at t = 1, 2 and 3 days. The yield of the cycloadducts ethyl 4,5-*trans*-3-ethyl-5-phenyl-4,5-dihydroisoxazole-4-carboxylate **(195)** and ethyl 4,5-*trans*-3-ethyl-4-phenyl-4,5-dihydroisoxazole-5-carboxylate **(196)** was calculated by comparison of signal intensities of the isoxazoline and methyl benzoate as 10 mg (29 μmol, 36%). The ratio of isomers was 2:1. These compounds were not isolated but were identified using the isoxazoline resonances in their ^{1}H NMR spectra by analogy with similar compounds in the literature[78, 139] and in the present study. The C5-H resonance of a 4-ethoxycarbonyl-5-phenylisoxazoline is generally in the region of δ5.9 - 6.2. The C4-resonance is generally in the region of δ3.9 - 4.5. The C5-H resonance of a 5-ethoxycarbonyl-4-phenylisoxazoline is generally in the region of δ4.8 - 5.1. The C4-resonance is generally in the region of δ4.5 - 4.9.

Ethyl 4,5-*trans*-3-ethyl-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (**195**): ^{1}H NMR: δ5.86 (1H, d, *J* = 8.5 Hz, C5-H), 3.99 (1H, d, *J* = 8.5 Hz, C4-H).

Ethyl 4,5-*trans*-3-ethyl-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (**196**): ^{1}H NMR: δ4.85 (1H, d, *J* = 6 Hz, C5-H), 4.51 (1H, d, *J* = 6 Hz, C4-H).

Synthesis of 3-acyl-4,5-dihydroisoxazolines - General procedure

To a solution of 1-chloro-1-(hydroxyimino)acetone (**151**) (0.50 g, 4.1 mmol) and dipolarophile (0.88 mmol) in dichloromethane (100 ml) was added triethylamine (1 ml, 0.73 g, 7.1 mmol). The reaction mixture was stirred for 24 hours and the solvent was removed *in vacuo*. The residue was then purified by flash chromatography (20% ethyl acetate in hexane).

Methyl 3-acetyl-4,5-dihydroisoxazole-5-carboxylate (197)

Dipolarophile: Methyl acrylate (**34**). Yield: 0.22 g (1.3 mmol, 31%). Appearance: colourless oil. ^{1}H NMR: δ5.20 (1H, t, *J* = 10 Hz, C5-H), 3.82 (3H, s, -OCH_3), 3.42 (2H, d, *J* = 10 Hz, C4-H_2), 2.52 (3H, s, CH_3CO-). MS: *m/z* 214, 197, 184, 172 $[M + H]^+$, 171 (rel. intensity: 3) $[M]^{+\cdot}$, 156 $[M - \cdot CH_3]^+$, 112 $[M - \cdot CO_2CH_3]^+$, 102, 84 (bp) $[M - \cdot COCO_2CH_3]^+$, 70, 59 $[CO_2CH_3]^+$. Anal. for $C_7H_9NO_4$: Calc: C: 49.12, H: 5.30, N: 8.18. Found: C: 48.85, H: 5.24, N: 8.07

(3-Acetyl-4,5-dihydroisoxazol-5-yl)methyl Acetate (199)

Dipolarophile: Allyl acetate (**166**). Yield: 0.11 g (0.58 mmol, 14%). Appearance: pale yellow oil. ^{1}H NMR: δ5.01 (1H, m, C5-H), 4.77 (1H, dd, *J* = 4, 12 Hz, C5-CH-O), 4.16 (1H, dd, *J* = 6, 12 Hz, C5-CH-O), 3.22 (1H, dd, *J* = 11, 18 Hz, C4-H), 2.96 (1H, dd, *J* = 8, 18 Hz, C4-H), 2.51 (3H, s, CH_3CO-), 2.10 (3H, s, CH_3CO_2-). ^{13}C NMR: δ192.91 (C3-$\underline{C}OCH_3$), 170.67 ($CH_3\underline{C}O_2$), 158.03 (C3), 81.25 (C5), 64.46 (C5-$\underline{C}H_2$-O), 34.21 (C4), 26.79 ($\underline{C}H_3CO_2$), 20.77 ($CO\underline{C}H_3$). MS (CI): *m/z* 203.1 (bp) $[MNH_4]^+$, 186.1 (rel. intensity: 54) $[MH]^+$, 169, 155, 142 $[M - CH_3CO_2H]^+$, 125, 112, 100 $[CH_2{=}CHCH_2O_2CCH_3]$, 82, 73. HR

MS: Calc. for $C_8H_{11}NO_4$: 185.068808. Found: 185.068829. This compound decomposed rapidly to give an orange/brown oil.

Methyl 3-acetyl-5-methyl-4,5-dihydroisoxazole-5-carboxylate (200)

Dipolarophile: Methyl methacrylate (**42**). Yield: 85 mg (0.45 mmol, 11%). Appearance: colourless oil: ^{1}H NMR: δ3.81 (3H, s, CH_3O-), 3.61 (1H, d, J = 18 Hz, C4-H), 3.02 (1H, d, J = 18 Hz, C4-H), 2.50 (3H, s, CH_3CO-), 1.68 (3H, s, -CH_3). ^{13}C NMR: δ199.79 ($CH_3\underline{C}O$-), 172.31 (-$\underline{C}O_2CH_3$), 158.62, (C3), 69.99 (C5), 54.26 (-OCH_3), 43.26 (C4), 27.77 (-$CO\underline{C}H_3$), 24.54 (C5-CH_3). MS: *m/z* 211, 186 (rel. intensity: 14) $[M + H]^+$, 185 $[M]^+$, 170 $[M - {}^{\cdot}CH_3]^+$, 153, 142 $[M - {}^{\cdot}COCH_3]^+$, 140, 125 (bp) $[M - CH_3CO_2H]^+$, 126 $[M - {}^{\cdot}CO_2CH_3]^+$, 125, 112, 102, 94, 84, 69, 59 $[CO_2CH_3]^+$. Anal. for $C_8H_{11}NO_4$: Calc: C: 51.89, H: 5.99, N: 7.56. Found: C: 51.78, H: 6.20, N: 7.54.

2-Oxopropanenitrile *N*-oxide (61) – ^{1}H NMR cycloaddition experiments

General procedure

A stock solution of 1-chloro-1-(hydroxyimino)acetone (**151**) (97 mg, 0.80 mmol) in *d*-chloroform (15 ml) was prepared. Aliquots of this stock solution (1.5 ml) were then transferred to round-bottomed flasks. To each aliquot was added a dipolarophile (0.11 mmol), methyl benzoate (9.1 μl, 10 mg) and triethylamine (15 μl, 11 mg, 80 μmol), in that order. The aliquots were then stirred for 5 min, washed with water (1 ml), separated and filtered though a short plug of silica into an NMR tube. ^{1}H NMR spectra were recorded immediately, then at t = 30 min. No change in the resonances was observed after 30 min.

Methyl 3-acetyl-4,5-dihydroisoxazole-5-carboxylate (197)

Dipolarophile: Methyl acrylate (**34**). Yield: 29%. ^{1}H NMR data are described above.

(3-Acetyl-4,5-dihydroisoxazol-5-yl)methyl Acetate (199)

Dipolarophile: Allyl acetate (**166**). Yield: 23%. ^{1}H NMR data are described above

*Methyl 3-acetyl-5-methyl-4,5-dihydroisoxazole-5-carboxylate (**200**)*

Dipolarophile: Methyl methacrylate (**42**). Yield: 27%. ^{1}H NMR data are described above.

Other dipolarophiles

No signals corresponding to cycloadducts were observed in the ^{1}H NMR spectra of the reaction mixtures of 2-oxopropanenitrile *N*-oxide (**61**) with ethyl *trans*-cinnamate (**70**), methyl crotonate (**49**), dimethyl maleate (**171**), or dimethyl fumarate (**169**).

Experimental - Chapter 7

Methyl 2-hydroxy-4-oxohexanoate (201)

Methyl 3-(2-methyl-1,3-dithian-2-yl)-4,5-dihydroisoxazole-5-carboxylate **(155)** (10 mg, 56 μmol) was added to a stirred suspension of Raney nickel (approx. 0.10 g) in methanol (5 ml). The reaction mixture was stirred under H_2 gas for 24 h. The reaction mixture was then filtered though celite and the celite washed with methanol. The solvent was removed *in vacuo*. ^{1}H NMR analysis of the residue showed signals representing a mixture of starting material and the title compound in a ratio of 1:1. ^{1}H NMR signals corresponding to the chemical shifts reported in the literature[140] of the compound **(201)** were observed at δ4.51 (1H, m, C2-H), 3.80, (~6H – co-integrated with methyl ester resonance of **(155)**), 2.94 (2H, ABX system (unresolved), C3-H_2), 2.48 (2H, q, J = 7 Hz, C5-H_2), 1.07 (3H, t, J = 7 Hz, C6-H_3).

Reaction of methyl 4,5-*cis*-5-(methoxycarbonyl)-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydroisoxazole-4-carboxylate (172) with Raney nickel

Methyl 4,5-*cis*-5-(methoxycarbonyl)-3-(2-methyl(1,3-dithian-2-yl))-4,5-dihydro-isoxazole-4-carboxylate **(172)** (0.10 g, 0.31 mmol) was dissolved in a mixture of THF (10 ml) and ethanol (20 ml). Raney nickel (1.5 g) in ethanol (5 ml) was added, and the mixture heated at reflux for 2 h. The reaction mixture was cooled to room temperature and filtered though celite. The filtrate was concentrated *in vacuo*, and the residue purified by flash chromatography (20% ethyl acetate in hexane). This procedure gave a mixture of unreacted starting material (34 mg), a clear oil which was believed to be the transesterification product **(204)** (15 mg) and a second clear oil believed to be the decomposition product **(203)** (10 mg).

Transesterification product (first oil) **(204)**: ^{1}H NMR: δ 5.22 (1H, d, J = 5 Hz, C5-H), 4.37 (1H, d, J = 5 Hz, C4-H), 4.20 (2H, q, J = 7 Hz, -OC$\underline{H}_2$CH$_3$), 3.70 (3H, s, -OCH$_3$),

3.3-3.45 (1H, m, dithiane C4-H_e), 3.0-3.1 (1H, m, dithiane C6-H_e), 2.5-2.65 (2H, m, dithiane C4,6-H_a), 2.0-2.1 (1H, m, dithiane C5-H_e), 1.6-1.75 (1H, m, dithiane C5-H_a), 1.64 (3H, s, dithiane $-CH_3$), 1.25 (3H, t, J = 7 Hz, $-OCH_2\underline{C}H_3$).

Methyl 3-amino-3-(2-methyl(1,3-dithian-2-yl))prop-2-enoate (second oil) (**203**): ^{1}H NMR: δ5.57 (1H, s, =CH-), 3.69 (3H, s, $-OCH_3$), 2.85-2.95 (2H, m, dithiane C4,6-H_e), 2.6-2.7 (2H, m, dithiane C4,6-H_a), 2.0-2.1 (1H, m, dithiane C5-H_e), 1.8-1.9 (1H, m, dithiane C5-H_a), 1.65 (3H, s, C6-H_3). MS: *m/z* 233 (rel. intensity: 64) $[M]^+$, 202 $[M - OCH_3]^+$, 200 $[M - SH]^+$, 172, 160, 142, 133 [methyldithianyl]$^+$, 127 (bp) [M – 1,2-dithiolanyl]$^+$, 112 [M – 1,2-dithiolanyl – CH_3]$^+$, 100 [M – methyldithianyl]$^+$, 68, 59 $[CO_2CH_3]^+$.

Methyl 2-hydroxy-4-oxononanoate (205)

Methyl 3-(2-butyl-1,3-dithian-2-yl)-4,5-dihydroisoxazole-5-carboxylate (**179**) (38 mg, 0.13 mmol) was added to a stirred suspension of Raney nickel (approx. 0.10 g) in methanol (5 ml). Acetic acid (10 mg) was added, and the reaction mixture was stirred under H_2 gas for 24 h. The reaction mixture was then filtered though celite and the celite was washed with methanol. The combined filtrates were partitioned between ether (10 ml) and water (10 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. This gave the title compound as a yellow oil (10 mg, 49 μmol, 38%).

^{1}H NMR: δ4.49 (1H, t, J = 5 Hz, C2-H), 3.79 (3H, s, $-OCH_3$), 2.93 (1H, ABX dd, J = 4, 16.5 Hz, C3-H), 2.88 (1H, ABX dd, J = 6, 16.5 Hz, C3-H), 2.44 (2H, t, J = 7 Hz, C5-H_2), 1.58 (2H, m, C6-H_2), 1.28 (4H, m, C7,8-H_2), 0.88 (3H, t, J = 7 Hz, C9-H_3). ^{13}C NMR: δ208.86 (C4=O), 174.11 ($-\underline{C}O_2CH_3$), 67.01 (C2-OH), 52.70 ($-CO_2\underline{C}H_3$), 45.72 (C3), 43.39 (C5), 31.22 (C6), 23.13 (C7), 22.39 (C8), 13.87 (C9). Anal. for $C_{10}H_{18}O_4$: Calc: C:59.39, H: 8.97, N: 0.00. Found: C: 59.73, H: 8.78, N: 0.00

Methyl 3-acetyl-4,5-dihydroisoxazole-5-carboxylate (197) *via* iron(III) nitrate nonahydrate deprotection of methyl 3-(2-methyl-1,3-dithian-2-yl)-4,5-dihydroisoxazole-5-carboxylate (155)

Iron(III) nitrate nonahydrate (62 mg, 0.15 mmol) was combined with silica (approx. 0.10 g), and hexane (3 ml) was added. The reaction mixture was heated to 50°C (hot water bath) and neat methyl 3-(2-methyl-1,3-dithian-2-yl)-4,5-dihydroisoxazole-5-carboxylate (**155**) (20 mg, 77 μmol) was added. The reaction mixture was stirred for 10 min and then was filtered though a glass sinter. The residue was washed thoroughly with ether. The filtrate was further filtered though a silica plug, and the solvent was removed *in vacuo*. This gave the title compound as a pale yellow oil (10 mg, 59 μmol, 77%).

Ethyl 4,5-*trans*-3-acetyl-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (208)

To neat ethyl 4,5-*trans*-3-(2-methyl(1,3-dithian-2-yl))-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (**175**) (76 mg, 0.22 mmol) was added a slurry of iron(III) nitrate nonahydrate (96 mg, 0.24 mmol) and silica (0.50 g) in hexane (3 ml), which had previously been warmed to 50°C. The reaction mixture was stirred at 50°C for 10 min and then filtered though a glass sinter and the residue was washed thoroughly with ether. The filtrates were combined and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (10% ethyl acetate in hexane) to give the title compound as a colourless oil (48 mg, 0.18 mmol, 84%).

^{1}H NMR: δ7.3-7.45 (5H, m, Ar H), 5.88 (1H, d, J = 8 Hz, C5-H), 4.25-4.30 (3H, m, overlapping C4-H and $-OC\underline{H}_2CH_3$), 2.57 (3H, s, CH_3CO), 1.30 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$). ^{13}C NMR: δ191.89 (C3-$\underline{C}OCH_3$), 168.64 (C4-CO_2), 155.53 (C3), 137.78 (Ar C1), 128.94 (*o*-Ar C), 125.71 (*m*-Ar C), 125.43 (*p*-Ar C), 89.48 (C5), 62.24 ($CO_2\underline{C}H_2CH_3$), 58.67 (C4), 26.75 (C3-CO$\underline{C}H_3$), 13.90 ($CO_2CH_2\underline{C}H_3$). MS: *m/z* 261 (rel. intensity: 3) $[M]^+$, 218 $[M - COCH_3]^+$, 192 $[M - COC{\equiv}N]^+$, 172, 146, 131, 128, 115, 105 (bp) $[PhCO]^+$, 77

$[Ph]^+$. Anal. for $C_{14}H_{15}NO_4$: Calc: C: 64.36, H: 5.79, N: 5.36. Found: C: 64.44, H: 6.18, N: 5.37.

Methyl 3-pentanoyl-4,5-dihydroisoxazole-5-carboxylate (209)

Iron(III) nitrate nonahydrate (56 mg, 0.14 mmol) was combined with silica (0.50 g), and hexane (2 ml) was added. The reaction mixture was heated to 50°C (hot water bath) and methyl 3-(2-butyl-1,3-dithian-2-yl)-4,5-dihydroisoxazole-5-carboxylate (**179**) (21 mg, 70 μmol) was washed into the reaction mixture with hexane (2 x 1 ml). The reaction mixture was stirred for 10 min at 50°C then was filtered though a glass sinter. The residue was washed thoroughly with ether. The filtrates were combined and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (10% ethyl acetate in hexane). This afforded the title compound as a pale yellow oil in a yield of 11 mg (52 μmol, 74%).

^1H NMR: δ5.18 (1H, t, J = 10 Hz, C5-H), 3.82 (3H, s, $-OCH_3$), 3.41 (2H, d, J = 10 Hz, C4-H_2), 2.91 (2H, t, J = 7.5 Hz, pentanoyl C2-H_2), 1.65 (2H, p, J = 7.5 Hz, pentanoyl C3-H_2), 1.36 (2H, sx, J = 7.5 Hz, pentanoyl C4-H_2), 0.92 (3H, t, J = 7.5 Hz, pentanoyl C5-H_2). ^{13}C NMR: δ194.93 (pentanoyl C1), 169.43 ($-\underline{C}O_2CH_3$), 156.79 (C3), 79.60 (C5), 52.91 ($-CO_2\underline{C}H_3$), 39.15 (C4), 36.52 (pentanoyl C2), 25.78 (pentanoyl C3), 22.16 (pentanoyl C4), 13.70 (pentanoyl C5). MS: *m/z* 213 (rel. intensity: 9) $[M]^+$, 196, 171, 156 $[M - {}^{\cdot}Bu]^+$, 143, 126, 110, 97, 85 $[M - {}^{\cdot}COBu]^+$, 70, 57 (bp) $[Bu]^+$. Anal. for $C_{10}H_{15}NO_4$: Calc: C: 56.33, H: 7.09, N: 6.57. Found: C: 56.33, H: 6.90, N: 6.66.

Ethyl 4,5-*trans*-3-pentanoyl-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (210)

To ethyl 4,5-*trans*-3-(2-butyl(1,3-dithian-2-yl))-5-phenyl-4,5-dihydroisoxazole-4-carboxylate (**180**) (0.10 g, 0.25 mmol) in hexane (10 ml) at 50°C was added a mixture of iron(III) nitrate nonahydrate (0.10 g, 0.25 mmol) and silica (1.0 g). The reaction mixture was stirred at 50°C for 20 min and then was filtered though a glass sinter. The residue was

washed thoroughly with ether. The filtrates were combined and the solvent was removed *in vacuo* to afford a yellow oil. The residue was purified by flash chromatography (10% ethyl acetate in hexane) to give the title compound as a colourless oil (38 mg, 0.12 mmol, 48%).

^{1}H NMR: δ7.3-7.45 (5H, m, Ar H), 5.86 (1H, d, J = 8 Hz, C5-H), 4.2-4.3 (3H, m, C4-H overlapped with $-OC\underline{H}_2CH_3$), 3.0 (1H, ABX dd, J = 8, 15 Hz, pentanoyl C2-H), 2.89 (1H, ABX dd, J = 7, 15 Hz, pentanoyl C2-H), 1.6-1.75 (2H, m, pentanoyl C3-H_2), 1.38 (2H, sx, J = 7 Hz, pentanoyl C4-H_2), 1.30 (3H, t, J = 7 Hz, $-OCH_2C\underline{H}_3$), 0.94 (3H, t, J = 7 Hz, pentanoyl C5-H_3). ^{13}C NMR: δ194.74 (pentanoyl C1), 168.68 ($-\underline{C}O_2CH_2CH_3$), 155.13 (C3), 137.86 (Ar C1), 128.89 (*o*-Ar C), 125.41 (*m*-Ar C), 125.27 (*p*-Ar C), 89.07 (C5), 62.15 ($-CO_2\underline{C}H_2CH_3$), 58.88 (C4), 39.02 (pentanoyl C2), 25.87 (pentanoyl C3), 22.10 (pentanoyl C4), 13.86 ($-CO_2CH_2\underline{C}H_3$), 13.65 (pentanoyl C5). MS: *m/z* 303 (rel. intensity: 26) $[M]^+$, 218 [M – pentanoyl]$^+$, 192, 176 $[PhCH{=}CHCO_2Et]^+$, 146, 131, 115, 105 (bp) [M – PhCO]$^+$, 85 [pentanoyl]$^+$, 77 $[Ph]^+$, 57 $[Bu]^+$. Anal. for $C_{17}H_{21}NO_4$: Calc: C: 67.31, H: 6.98, N: 4.62. Found: C: 67.51, H: 7.19, N: 4.60.

Ethyl 4,5-*trans*-3-pentanoyl-4-phenyl-4,5-dihydroisoxazole-5-carboxylate (211)

To ethyl 4,5-*trans*-3-(2-butyl(1,3-dithian-2-yl))-4-phenyl-4,5-dihydroisoxazole-5-carboxylate **(181)** (35 mg, 88 μmol) in hexane (2 ml) at 50°C was added a slurry of iron(III) nitrate nonahydrate (36 mg, 88 μmol) and silica (0.25 g) in hexane (3 ml), which had previously been warmed to 50°C. The reaction mixture was stirred at 50°C for 20 min and then filtered though a glass sinter and the residue was washed thoroughly with ether. The filtrates were combined and the solvent was removed *in vacuo* to afford a yellow oil. This oil was partitioned between water and dichloromethane, and the organic extract was dried over anhydrous magnesium sulfate, filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (10% ethyl acetate in hexane) to give the title compound as a colourless oil (14 mg, 46 μmol, 53%).

^{1}H NMR: δ7.1-7.4 (5H, m, Ar H), 5.04 (1H, d, J = 5 Hz, C5-H), 4.82 (1H, d, J = 5 Hz, C4-H), 4.29 (2H, q, J = 7 Hz, -OC$\underline{H}_2$CH$_3$), 3.01 (1H, ABX dd, J = 8, 16 Hz, pentanoyl C2-H), 2.81 (1H, ABX dd, J = 7, 16 Hz, pentanoyl C2-H), 1.5-1.6 (2H, pentanoyl C3-H), 1.2-1.4 (5H, m, -OCH$_2$C$\underline{H}_3$ overlapped with pentanoyl C4-H), 0.86 (3H, t, J = 7 Hz). ^{13}C NMR: 194.08 (pentanoyl C1), 168.50 (–$\underline{C}$O$_2$CH$_2$CH$_3$), 158.55 (C3), 137.04 (Ar C1), 129.15 (*o*-Ar C), 128.17 (*m*-Ar C), 127.05 (*p*-Ar C), 87.55 (C5), 62.19 (C4), 55.65 (–CO$_2\underline{C}$H$_2$CH$_3$), 39.55 (pentanoyl C2), 25.65 (pentanoyl C3), 21.99 (pentanoyl C4), 13.98 (–CO$_2$CH$_2\underline{C}$H$_3$), 13.62 (pentanoyl C5). MS: *m/z* 303 (rel. intensity: 30) $[M]^{+}$, 230 $[M - CO_2CH_2CH_3]^{+}$, 202, 173, 146, 131, 117, 85 (bp) $[pentanoyl]^{+}$, 57 $[Bu]^{+}$. Anal. for $C_{17}H_{21}NO_4$: Calc: C: 67.31, H: 6.98, N: 4.62. Found: C: 67.35, H: 7.00, N: 4.72

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